Study Title

A multicenter, multinational, randomized, double-blind, pharmacokinetic and pharmacodynamic (PK/PD) dose-finding study of oral netupitant administered concomitantly with oral palonosetron in pediatric cancer patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

Study Number	NEPA-15-31
Protocol Version	Final (v. 5.0)
Protocol Date	11 Feb 2019
Sponsor	Helsinn Healthcare SA Via Pian Scairolo 9, 6912 Lugano/Pazzallo, Switzerland
IND Number:	73,493
CRO	PSI CRO AG Baarerstrasse 113a, 6300 Zug, Switzerland

The clinical trial will be conducted, and essential study documentation archived, in compliance with this protocol, applicable SOP's and standards, which incorporate the requirements of the ICH Guideline for Good Clinical Practice.

Document History

With respect to final protocol version 3.0, dated 07 Feb 2017, the following changes were introduced in version 4.0:

Inclusion criterion #4 was updated to add imaging for initial diagnosis of nephrobastoma since European standard of care for nephroblastoma consists of adjuvant chemotherapy followed by nephrectomy and histology reports could be received several weeks later, after the patient completes the study.

Inclusion criteria were updated to include specific thresholds for laboratory parameters (ALT, AST, bilirubin, eGFR) as recommended by DSMB. Schwartz equation was provided as a recommended tool to calculate eGFR.

Exclusion criteria were updated to include specific thresholds for QTc parameters, as well as other safety precautions related to patients' concomitant conditions and laboratory abnormalities, as recommended by DSMB.

Clarifications related to the assessment of patients' eligibility based on local laboratory parameters/automated interpretation of cardiac parameters by ECG machine were added to the corresponding eligibility criteria sections and throughout the protocol as applicable.

Time window for palonosetron administration (interval after netupitant administration) was added.

Administrative changes in the names of service provider companies and their representatives were made.

A misprint in footnote #3 of the Flow Chart on page 27 was corrected.

The definitions of emetic episode and regurgitation were added.

Clarification on criteria for evaluating chemotherapy schedule (single day vs. multiple days) was added.

Information on emetogenicity of intravenous temozolomide was provided in Appendix 2 following POGO Guideline.

With respect to final protocol version 4.0, dated 06 Nov 2017, the following changes have been introduced in version 5.0:

Following a specific recommendation from FDA (US FDA Deferral Extension letter dated 15 Jan 2019), for purposes of facilitating enrollment in the study, enrollment of the age cohorts 3 < 6 months and 1 < 3 months and birth < 1 month is allowed in parallel (instead of sequentially), keeping the original treatment dose escalation scheme (i.e., first lowest doses are to be given in parallel in all remaining age cohorts, then highest doses are to be given in parallel in all the remaining age cohorts). This approach was also endorsed by DSMB members.

In Section 4.10.3 Other Prior and Concomitant Medications, an additional clarification was provided concerning the use of any drugs or substances known to be inhibitors of CYP3A4 and CYP2D6 enzymes (including any of the narrow therapeutic range CYP3A4 substrates), which are to be avoided within 1 week prior to Day 1 or during the overall

study period (until Visit 5 inclusive). It has also been clarified that the intake of drugs or substances known to be inducers of CYP3A4 enzymes within 4 weeks prior to the dosing day or use of such medications during the overall study period (until Visit 5 inclusive) is not permitted.

Consistent with the regulatory recommendations set forth in document entitled "Ethical considerations for clinical trials on medicinal products conducted with minors, developed by the European Commission expert group on clinical trials", the volume of blood collected for the purposes of the clinical study in small children with body weight less than 5.4 kg should be limited. Therefore, Section 6.1 Pharmacokinetics Assessments was updated as follows: for small children less than 5.4 kg the volume of PK samples was adjusted from 2 mL to 1 mL and the total blood volume collected per patient has to be approximately 3.0 mL. Moreover, each plasma sample has to be immediately divided into 2 aliquots in the pre-labeled polypropylene tubes: 1 aliquot ≥130 µL for the analysis of netupitant and its metabolites (M1, M2 and M3), and 1 aliquot of ≥250 µL for the analysis of palonosetron – no back-up samples are to be obtained.

In Section 11. References, the references 14 and 17 of the Investigator's Brochures for Palonosetron and Oral NEPA FDC respectively were updated to be with the latest versions.

Finally, in General information some information was corrected (e.g., phone numbers, a new Sponsor's Medical Expert for the study) or updated (changed company the name of bioanalytical lab was changed).

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Study Title

A multicenter, multinational, randomized, double-blind, pharmacokinetic and pharmacodynamic (PK/PD) dose-finding study of oral netupitant administered concomitantly with oral palonosetron in pediatric cancer patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

Study Number NEPA-15-31

I have read and understood all pages of this clinical trial protocol and appendices and I agree that they contain all information required to conduct this trial. I agree to conduct the trial as outlined in the protocol and to comply with all terms and conditions set out therein. I confirm that I will conduct the trial in accordance with local regulations, ICH GCP guidelines and the provisions of the Declaration of Helsinki. I will direct, assist and oversee sub-Investigator(s) and other relevant staff members under my control and will ensure that all trial staff members have access to copies of this protocol and to all information relating to preclinical and prior clinical experience (e.g., Investigator's Brochure), ICH GCP guidelines, local regulations and the Declaration of Helsinki to enable them to work in accordance with the provisions of these documents.

I agree that all documentation supplied to me by Helsinn and CRO concerning this trial will be kept in the strictest confidence.

_____ _____

(Signature) (Date)

Printed Name:

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TABLE OF CONTENTS

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STUDY SYNOPSIS

Study Title	A multicenter, multinational, randomized, double-blind, pharmacokinetic and pharmacodynamic (PK/PD) dose-finding study of oral netupitant administered concomitantly with oral palonosetron in pediatric cancer patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy.
Study Number	NEPA-15-31
Sponsor	Helsinn Healthcare SA, Via Pian Scairolo 9, 6912 Lugano/Pazzallo, Switzerland
Countries and Sites	A minimum of approximately 16 sites in USA, Russia, Ukraine and Serbia; more sites and/or countries may be added if necessary.
Clinical Phase	Phase 2
Indication	Chemotherapy-induced nausea and vomiting (CINV)
Study Design	This is a multicenter, multinational, randomized, double-blind, stratified (by age class; by emetogenicity; by chemotherapy schedule), dose-finding study involving two treatment groups receiving a single oral dose of netupitant administered concomitantly with a single oral dose of 20 µg/kg oral palonosetron (up to a maximum of 1.5 mg). Netupitant dose treatment groups: – Treatment group 1: 1.33 mg/kg up to a maximum of 100 mg. For patients aged < 3 months, the netupitant dose will be 0.8 mg/kg. – Treatment group 2: 4 mg/kg up to a maximum of 300 mg. For patients aged < 3 months, the netupitant dose will be 2.4 mg/kg. Pediatric population will be split in the following age classes: – Birth to < 1 month – 1 month to < 3 months – 3 months to < 6 months – 6 months to < 12 months – 1 year to < 2 years – 2 years to < 5 years – 5 years to < 12 years – 12 years to < 18 years. At the beginning of the study, enrolment is open only to: – patients aged ≥ 1 year, who will be randomized to one of the two

	netupitant doses – patients aged 6 months to < 12 months who will be treated with the netupitant lower dose (1.33 mg/kg). At the beginning of the study three patients aged **6 to < 12 months** will be first enrolled in the lower netupitant dose group (1.33 mg/kg). As soon as these first 3 patients have completed the study, without safety and tolerability concerns as assessed by Data Safety Monitoring Board (DSMB), enrolment in the higher netupitant dose group (4 mg/kg) of the same age class (6 to < 12 months) can start. As soon as 6 patients in the age class 6 to < 12 months (3 patients for each netupitant dose group) have completed the study without safety and tolerability concerns, decision by DSMB will have to be taken whether a) all remaining patients 6 to <12 months can be randomized to one of the two netupitant treatment doses and start the assigned treatment, and b) the lower age class **3 to < 6 months** may start the treatment with the lower dose. The enrollment of the remaining cohorts will occur in parallel keeping the original treatment dose escalation scheme: 3 patients will be first treated with the lower netupitant dose. As soon as these first 3 patients will have completed the study and no safety and tolerability concerns are shown, as assessed by the DSMB, enrolment in the higher dose group in the same age class will start.

Study Objectives	Primary Objective: To investigate the PK/PD correlation between netupitant exposure and antiemetic efficacy after a single oral netupitant administration, concomitantly with oral palonosetron in pediatric cancer patients receiving moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) treatments. Efficacy parameter to be used in the correlation is the proportion of patients with complete response (CR, i.e., no emetic episodes and no rescue medication) during the delayed phase (> 24-120 h after the start of chemotherapy on Day 1). Secondary Objectives: To assess the safety and tolerability after single oral administration of netupitant given concomitantly with a single oral administration of palonosetron. To evaluate the PK profile of oral palonosetron at the fixed dose of 20 µg/kg in pediatric patients with the concomitant administration of netupitant.
Treatment Groups	A total of 92 pediatric cancer patients will be enrolled to one of the two treatment groups (46 patients in each treatment group): – Treatment group 1 – patients ≥ 3 months of age will receive a single oral netupitant dose of 1.33 mg/kg (up to a maximum of 100 mg for patients weighting 75 kg or more) concomitantly with a single oral palonosetron dose of 20 µg/kg (up to a maximum of 1.5 mg for patients weighting 75 kg or more). For patients < 3 months of age the netupitant dose will be 0.8 mg/kg. – Treatment group 2 – patients ≥ 3 months of age will receive a single oral netupitant dose of 4 mg/kg (up to a maximum of 300 mg for patients weighting 75 kg or more) concomitantly with a single oral palonosetron dose of 20 µg/kg (up to a maximum of 1.5 mg for patients weighting 75 kg or more). For patients < 3 months of age the netupitant dose will be 2.4 mg/kg.
Dosage and Administration	In order to allow the administration of the study drug according to the two netupitant treatment doses, three Investigational Medicinal Products (IMPs) will be used in the study: IMP 1: Oral liquid formulation of netupitant (100 mg/7 mL) suitable for use in all pediatric age classes. Netupitant will be administered based on the body weight as a single oral dose 1 h (± 10 minutes) prior to start of emetogenic chemotherapy (HEC or MEC) on Day 1. IMP 2: Oral liquid formulation of netupitant (300 mg/7 mL) suitable for use in all pediatric age classes. Netupitant will be administered

	based on the body weight as a single oral dose 1 h (± 10 minutes) prior to start of emetogenic chemotherapy (HEC or MEC) on Day 1. IMP 3: Palonosetron will be administered orally using the 0.75 mg/5 mL solution for IV use. Palonosetron will be administered based on the body weight, immediately (within 5 minutes) after netupitant, i.e., 1 h (± 10 minutes) prior to start of emetogenic chemotherapy (HEC or MEC) on Day 1.
Target Study Population	Male and female pediatric cancer patients from birth up to < 18 years, scheduled to receive HEC or MEC to be administered as single day chemotherapy on Day 1 only or for multiple days.
Number of Patients	A total of 92 pediatric patients will be enrolled to one of the two treatment groups (i.e., 46 in each treatment group). For each age class included in the stratification, the relevant planned number of patients to be enrolled is provided below. - Birth to < 1 month: 12 patients - 1 to < 3 months: 12 patients - 3 to < 6 months: 8 patients - 6 to < 12 months: 8 patients - 1 to < 2 years: 8 patients - 2 to < 5 years: 12 patients - 5 to < 12 years: 16 patients - 12 to < 18 years: 16 patients

Stratification	The study is stratified by:
	
	- Age class:
	  • Birth to < 1 month
	  • 1 to < 3 months
	  • 3 to < 6 months
	  • 6 to < 12 months
	  • 1 to < 2 years
	  • 2 to < 5 years
	  • 5 to < 12 years
	  • 12 to < 18 years
	- Emetogenicity:
	  • HEC
	  • MEC
	- Chemotherapy schedule:
	  • HEC/MEC on Day 1 only
	  • HEC/MEC on multiple days
	
	Note that the Emetogenicity and Chemotherapy schedule strata do not apply for patients < 1 year of age (i.e., all age classes < 12

	months).
Chemotherapy Regimens	Any chemotherapy regimen of moderate or high emetogenicity to be administered as single day chemotherapy on Day 1 only or on multiple days can be used in this study. For consistency of interpretation, "multiple days" schedule would include regimens with additional HEC/MEC given between Day 1 and Day 6 (within 120 hours from the start of first HEC/MEC administration on Day 1). Any low emetogenic chemotherapy (LEC) agent or minimally emetogenic chemotherapy agent given, as part of the aforementioned chemotherapy regimens using HEC or MEC, is allowed at any time.
Rescue Medication	Rescue medication is defined as any medication taken to alleviate nausea or vomiting (i.e., with indication nausea or vomiting) during the period from start of HEC or MEC to 120 h later. The choice of rescue medication will be at the discretion of the Investigator. Use of palonosetron or netupitant other than study drugs administration is not permitted. Use of metoclopramide is not allowed.
Inclusion Criteria	The following inclusion criteria must be checked prior to inclusion: 1. Signed written informed consent by parent(s)/legal guardians of the pediatric patient in compliance with the local laws and regulations. In addition signed children's assent form according to local requirements. 2. Male or female in- or out-patient from birth to < 18 years at the time of randomization. 3. Patient weight at least 3.3 kg. 4. Naïve or non-naïve patient with histologically, and/or cytologically (or imaging in the case of brain tumors or nephroblastoma) confirmed malignant disease. 5. Scheduled and eligible to receive at least one moderately or highly emetogenic chemotherapeutic agent on Day 1 only or for multiple days. 6. For patient aged ≥ 10 years: Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2. 7. Adequate hepatic function defined as serum ALT and AST ≤ 2.5 ULN, and total bilirubin ≤ 1.5 ULN. 8. Adequate renal function defined as estimated glomerular filtration rate (eGFR) ≥ 70 ml/min/1.73m^2 (≥ 50 ml/min/1.73m^2

	for children < 3 months old). The eGFR should be calculated using the modified Schwartz equation. 9. For patient with known history or predisposition to cardiac abnormalities: in the Investigator's opinion the history/predisposition should not jeopardize patient's safety during the study. 10. If the patient is female, she shall: a) not have attained menarche yet or b) have attained menarche and have a negative pregnancy test at the screening visit and at Day 1. 11. Male or female fertile patient using reliable contraceptive measures (such measures, for patient and sexual partner, include: implants, injectables, combined oral contraceptives, intrauterine devices, vasectomized/sterilized partner, use of a double-barrier method or sexual abstinence). The patient and his/her parent(s)/legal guardians must be counseled on the importance of avoiding pregnancy before or during the study. All inclusion criteria will be checked at screening visit (Visit 1). Inclusion criteria #3, 5, 10 will be re-checked at Day 1 (Visit 2). Local laboratory results from an appropriately certified local laboratory could be used at the discretion of Investigator to evaluate patients' eligibility.
Exclusion Criteria	The following exclusion criteria must be checked prior to inclusion: 1. The patient and/or parents/caregivers are expected by the Investigator to be non-compliant with the study procedures. 2. Patient has received or is scheduled to receive total body irradiation, total nodal irradiation, upper abdomen radiotherapy, half or upper body irradiation, radiotherapy of the cranium, craniospinal regions, head and neck, lower thorax region or the pelvis within 1 week prior to study entry (Day 1) or within 120 h after start of chemotherapy administration on Day 1. 3. Known history of allergy to any component or other contraindications to any NK_1 or 5-HT_3 receptor antagonists. 4. Active infection. 5. Any illness or condition that, in the opinion of the Investigator, may pose unwarranted risks in administering the investigational product to the patient. 6. Patient suffering from ongoing vomiting from any organic etiology (including patients with history of gastric outlet obstruction or intestinal obstruction due to adhesions or

	volvulus, patients with a symptomatic CNS tumor causing nausea and/or vomiting) or patient with hydrocephalus. 7. Patient who experienced any vomiting, retching, or nausea within 24 h prior to the administration of the study drug (note: functional vomiting for infants, which is normally seen during the first 3 months of life, is not to be considered as vomiting). 8. Patient who received any drug with potential anti-emetic effect within 24 h prior to the start of reference chemotherapy, including but not limited to: - NK_1- receptor antagonists (e.g., aprepitant or any other new drug of this class); - 5-HT_3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron, tropisetron, ramosetron); - Benzamides (e.g., metoclopramide, alizapride); - Phenothiazines (e.g., prochlorperazine, promethazine, perphenazine, fluphenazine, chlorpromazine, theithylperazine); - Benzodiazepines initiated 48 h prior to study drug administration or expected to be received within 120 h following initiation of chemotherapy, except for single doses of midazolam, temazepam or triazolam; - Butyrophenones (e.g., droperidol, haloperidol); - Anticholinergics (e.g., scopolamine, with the exception of inhaled anticholinergics for respiratory disorders e.g., ipratropium bromide); - Antihistamines (e.g., diphenhydramine, cyclizine, hydroxyzine, chlorphenhyramine, dimenhydrinate, meclizine); - Domperidone; - Mirtazapine; - Olanzapine; - Prescribed cannabinoides (e.g., tetrahydrocannabinol, nabilone); - Over the Counter (OTC) antiemetics, OTC cold or OTC allergy medications; - Herbal preparations containing ephedra or ginger. 9. Patient who received palonosetron within 1 week prior to

	administration of study drug. 10. Patient who has been started on systemic corticosteroid therapy within 72 h prior to study drug administration or is planned to receive a corticosteroid as part of the chemotherapy regimen. Exceptions: - Patient who is receiving chronic (> 72 h), daily steroid therapy can be enrolled provided the steroid dose is not > 0.14 mg/kg (up to 10 mg) of prednisone daily or equivalent. - For supportive care, patient is permitted to receive a single dose of corticosteroid within the 72 h prior to study drug administration (but not < 12 h prior to study drug administration) provided it is less than the equivalent of 20 mg of prednisone. 11. Patient aged < 6 years who received any investigational drug (defined as a medication with no marketing authorization granted for any age class and any indication) within 90 days prior to Day 1, or patient aged ≥ 6 years who received any investigational drug within 30 days prior to Day 1 or is expected to receive investigational drugs prior to study completion. 12. Intake of alcohol, food or beverages (e.g., grapefruit, cranberry, pomegranate and aloe vera juices, German chamomile) known to interfere with either CYP3A4 or CYP2D6 metabolic enzymes within 1 week prior to Day 1 and during the overall study period. 13. Use of any drugs or substances known to be strong or moderate inhibitors of CYP3A4 and CYP2D6 enzymes within 1 week prior to Day 1 or planned to be used during the overall study period. 14. Use of any drugs or substances known to be CYP3A4 substrates with narrow therapeutic range within 1 week prior to Day 1, or planned to be used during the overall study period. 15. Use of any drugs or substances known to be inducers of CYP3A4 enzymes within 4 weeks prior to Day 1 or planned to be used during the overall study period. 16. Lactating female patient. 17. Patient with clinically relevant Grade 3 or 4 non-hematological abnormal laboratory values.

	20. Enrolment in a previous study with netupitant (either alone or in combination with palonosetron). 21. Marked baseline prolongation of QTc interval [QTcB or QTcF > 460 msec] at screening. NOTE: Exclusion criteria ## 18 and 19 were skipped intentionally to maintain consistency in exclusion criteria numbering between protocol amendments. All exclusion criteria will be checked at screening visit (Visit 1). Exclusion criteria #2, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 17, 21 will be re-checked at Day 1 (Visit 2). In case of ERT central ECG report pending, the assessment of compliance with exclusion criterion #21 could be made based on automatic interpretation of QTcB and QTcF results by ECG machine at the discretion of Investigator. All eligible patients must be approved for randomization by authorized Medical Monitor.
Study Duration	The planned duration of the study for each pediatric patient is a maximum of 31 days, which includes screening up to 14 days before randomization (up to 7 days for patients aged < 2 years), day of enrolment/randomization, administration of study drugs and chemotherapy (Study Day 1), and the PK visit (Study Days 2 to 5). The final visit will be 6 to 8 days after study drug administration, and a follow up visit/telephone contact will be performed between 14 and 17 days after study drug administration.
Study Endpoints	<u>Primary Endpoint:</u> PK/PD relationship between netupitant exposure (AUC, C_{max}) and antiemetic efficacy in the delayed phase after a single oral netupitant administration, concomitantly with oral palonosetron, in pediatric cancer patients receiving HEC or MEC treatments. Efficacy parameter to be used in the correlation is the proportion of patients with complete response (CR, i.e., no emetic episodes and no rescue medication) during the delayed phase (> 24-120 h after the start of chemotherapy on Day 1). <u>Secondary Endpoints:</u> - Pharmacokinetic (PK) endpoints: • AUC, C_{max}, t_{max} and $t_{1/2}$ of netupitant, netupitant metabolites M1, M2, M3, and palonosetron. - Pharmacodynamic (PD) endpoints: • proportion of patients with complete response (CR, i.e., no emetic episodes and no rescue medication) during the delayed (> 24-120 h), acute (0-24 h) and overall phases (0-120 h) after

	start of chemotherapy administration on Day 1. • proportion of patients with no emetic episodes during the delayed (>24-120 h), acute (0-24 h) and overall phases (0-120 h) after start of chemotherapy administration on Day 1. • proportion of patients with no rescue medication during the delayed (>24-120 h), acute (0-24 h) and overall phases (0-120 h) after start of chemotherapy administration on Day 1.
Assessment of the Pharmacokinetic Profile	The PK profiles of netupitant, its active metabolites M1, M2, M3, and palonosetron will be evaluated in pediatric cancer patients according to a sparse sampling schedule and a population PK approach. A single blood sample will be collected from each patient in each of the following time windows: • Pediatric patients ≥ 5 years: from 2 to 8 h, from 24 to 48 h, from 72 to 96 h, and from 120 to 168 h after netupitant administration. • Pediatric patients < 5 years: from 2 to 8 h, from 24 to 48 h, and from 120 to 168 h after netupitant administration. The nominal number of plasma samples collected from all patients after each of the two treatments will be 154. The expected total number of plasma samples collected after the two treatments will be 308. The volume of each blood sample will be 2.0 mL. For patient with body weight < 5.4 kg, the volume of each blood sample will be 1.0 mL. Data modelling will be based on a previous population PK study in adults receiving oral NEPA (study NETU-10-02). If the same structural models apply to the pediatric population, the typical values (TV) of the following structural model parameters will be assessed for netupitant and palonosetron: - Ka: absorption rate constant for netupitant or formation rate constant for netupitant metabolites - t_{lag}: lag time - Vi/F: apparent volume of compartment i, i.e., central and peripheral compartment(s), for extravascular administration - CL/F: apparent systemic clearance for extravascular administration - Q/F: inter-compartmental clearance F is the absolute oral bioavailability for the parent compounds netupitant and palonosetron. Different structural models could also be explored for netupitant, its

	metabolites, and palonosetron according to the findings of the present PK/PD study in pediatric patients after oral administration of netupitant and palonosetron. The final model parameters will reflect the model structure and include possible continuous or categorical covariates that significantly correlate with PK parameters and explain inter-subject variability. Individual model-predicted PK parameter values will be estimated from the final population pharmacokinetic models, based on mean population parameter values (typical values, TVs) and on the individual random effect (ηi). From final model parameters, individual plasma concentration-time profiles will be simulated and secondary PK parameters such as C_{max}, t_{max}, AUC and $t_{1/2}$ estimated by non-compartmental methods.
Efficacy Assessments	Efficacy assessments will be collected through a paper diary, which will be used to record emetic episodes and use of rescue medication. Patients, parent's guardians or caregivers should complete the diaries.
Safety Assessments	Safety assessments will consist of physical examination (PE) and clinical laboratory tests (serum chemistry, hematology, urinalysis): these assessments will be performed at screening and at final visit. Moreover, vital signs measurements (pulse rate, systolic and diastolic blood pressure) and 12-lead ECGs (single recordings) will be obtained at screening, on Day 1 at 4-6 h after study drug administration, and at final visit. Adverse events (AEs) will be monitored throughout the study. During the conduct of the study, a Data Safety Monitoring Board (DSMB) will review safety data, as foreseen by the study design and at periodical intervals.
PK/PD Correlation	PK/PD relationships between predicted individual exposure metrics (C_{max} and AUC) of netupitant at different dose levels versus efficacy (CR delayed) will be investigated via graphical exploratory analyses. In addition, a logistic regression analysis will be used to link the exposure metrics to categorical response (CR delayed). The dose-exposure relationship and the PK/PD correlation (exposure-response relationship) for netupitant in pediatric cancer patients will support the dose selection for a subsequent Phase 3 study.
Pharmacokinetic Analyses	Exploratory analyses will be applied to evaluate in the pediatric population the PK characteristics of netupitant (and its metabolites) and palonosetron after concomitant administration. The initial population PK models (base models) will be developed by comparing structural models and random error models based on

	parameters such as the objective function values, the log-likelihood values, the Akaike's and the Bayesian's Information Criteria (AIC and BIC), the residual errors, the random distribution in conditional weighted residual plots, the graphical correlation between the observed versus predicted concentration values. The final population PK models will include possible additional fixed effects represented by relevant covariates that will prove to correlate with one or more population PK parameters and contribute to significantly explain and minimize the inter-subject variability. The final model will be qualified via a visual predictive check. Inter-subject / inter-occasion variability (level 1 random-effect) and observation-level random error (level 2 random effect) will also be modeled. Individual model-predicted PK parameter values will be estimated from the final population pharmacokinetic models, based on mean population parameter values (typical values, TVs) and on the individual random effect (ηi). From final model parameters, individual plasma concentration-time profiles will be simulated and secondary PK parameters such as C_{max}, t_{max}, AUC and $t_{1/2}$ estimated by non-compartmental methods. Mean and coefficient of variation (CV) of the pharmacokinetic parameters will be calculated from the individual predictions. The effect of continuous and categorical covariates on the PK parameter variability will be evaluated by step-wise forward addition and backward elimination procedures. Continuous covariates will include at least age, BW, albumin, total bilirubin, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP). Categorical covariates will include at least gender, HEC/MEC, chemotherapy schedule, rescue medication (yes/no), concomitant medications. Data from previous population PK study NETU-10-02 in adult cancer patients receiving oral NEPA FDC administration (300mg netupitant/0.5mg palonosetron) will be used as prior information and included in the analysis.

Efficacy Analysis	All results will be interpreted in a descriptive manner, since the study is not powered to compare the treatment groups for the efficacy assessments. For each phase (delayed, acute, and overall), numbers and percentages (including 95% CI) of patients with complete response, with no emetic episodes and no rescue medication will be summarized by treatment. The difference in response rate between the two groups and relevant 95% CI will be provided as well. Efficacy analysis will be presented for the overall population and by strata.
Safety Analysis	All AEs will be listed by SOC, described and summarized by frequency tables. Summaries will be made by treatment arm with respect to the percentage of patients having at least one occurrence of that event during the study and the total number of events. For safety analysis, the laboratory data will be analyzed and described as follows: listings (including flag for values outside the normal range), count (number and percentage) of value below, within and above normal range, descriptive statistics for change from baseline values. Shift tables with respect to normal range (Low/Normal/High) will be presented. ECG data will be summarized highlighting differences from baseline for quantitative variables and frequencies of treatment emergent abnormalities. Vital signs will be summarized using descriptive statistics for observed values and change from baseline, in addition to being listed. Safety analysis will be presented for the overall safety population and by strata.

FLOW CHART

Visit	**V1**	**V2**	**V3**	**V4**	**V5**[14]
Timepoint (Day)	-14 to -1; -7 to -1 for < 2 years	1	2, 3, 4 and/or 5	6, 7 or 8	14 [+3]
Assessments	**Screening**	**Randomization / Treatment**	**PK Visit**	**Final Visit**	**Follow up**
Informed Consent/Assent	X				
Inclusion/Exclusion Criteria	X	X[10]			
Demography, medical and surgical history (including current cancer history, naivety to chemotherapy)	X				
History of nausea and vomiting in previous chemotherapy[1]	X				
ECOG status[2]	X				
Hematology, Serum chemistry, Urinalysis[3]	X			X	
Pregnancy test (urine)[4]	X	X			
Physical examination	X			X	
Vital signs	X	X[11, 12]		X[11]	
Height/Length	X				
Weight	X	X			
12-lead ECG[5]	X	X[12, 13]		X[13]	
Randomization / Treatment assignment		X			
Study drugs administration[6]		X			
Record efficacy parameters			Recording up to 120h		
Patient Diary	Instruction		Filled in up to 120h		
Collection of Patient Diary[7]				X	
Prior and concomitant medication recording	X	X	X	X	X
Adverse event monitoring[8]	X	X	X	X	X
PK sampling[9]		X	X	X	

1 Only if applicable (for non-naïve patients).

2 ECOG status will be assessed for patients aged ≥ 10 years.

3 Whole blood, serum and urine samples will be sent to a central laboratory. Urine sample will be obtained only if the patient is capable of providing a urine sample. At the final visit (Visit 4) only, serum sample will also be used for pregnancy test.

4 For female patients having reached menarche only. If screening is performed on Day -1, it is not necessary to repeat the test on Day 1.

5 12-lead ECG (single recording) will be evaluated in a central reading facility.

6 Study drugs will be administered as follows:

- Netupitant will be administered based on the body weight as a single oral dose 1 h (± 10 minutes) prior to the start of emetogenic (HEC or MEC) chemotherapy on Day 1.
- Oral palonosetron will be administered based on weight immediately (within 5 minutes) after netupitant, i.e., 1 h (± 10 minutes) prior to start of emetogenic (HEC or MEC) chemotherapy on Day 1.
- Any LEC or minimally emetogenic agent given, as part of the aforementioned chemotherapy regimens using HEC or MEC, is allowed at any time during the study and does not have any impact on the time of study drugs administration.

7 The patient will be instructed to bring the diary back to the site at each visit so that the Investigator is able to ensure it has been completed in a timely and appropriate manner.

8 Starting at the screening visit, immediately after informed consent/assent, up to the follow up visit/telephone contact.

9 A single blood sample will be collected from each patient in each of the following time windows:

- Pediatric patients ≥ 5 years: from 2 to 8 h, from 24 to 48 h, from 72 to 96 h, and from 120 to 168 h after netupitant administration.
- Pediatric patients < 5 years: from 2 to 8 h, from 24 to 48 h, and from 120 to 168 h after netupitant administration.

10 On Day 1, inclusion criteria #3, 5, 10 and Exclusion criteria #2, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 17, 21 should be re-checked prior to randomization/enrollment (local laboratory results from an appropriately certified local laboratory could be used at the discretion of Investigator to evaluate patients' eligibility; in case of ERT central ECG report pending, the assessment of compliance with exclusion criterion #21 could be made based on automatic interpretation of QTcB and QTcF results by ECG machine at the discretion of Investigator).

11 Vital signs to be measured before PK sampling or at least 30 minutes after PK sampling.

12 Vital signs and 12-lead ECGs (single recording) will be obtained at 4-6 h after study drugs administration.

13 12-lead ECGs (single recording) to be obtained before PK sampling or at least 30 minutes after PK sampling.

14 Follow up Visit / Telephone Contact (14 [+3] days after drug administration).

LIST OF ABBREVIATIONS

5-HT_3	5-hydroxytryptamine
ADE	Age-dependent exponent
ADL	Activities of Daily Living
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse Event
AIC	Akaike's Information Criteria
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
API	Active Pharmaceutical Ingredients
AST	Aspartate aminotransferase
AUC	Area Under the Plasma Concentration-Time Curve
BIC	Bayesian's Information Criteria
BW	Body weight
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CL	Systemic (or total) Clearance
CK	Creatine kinase
CL/F	Apparent systemic clearance for extravascular administration
CL_R	Renal clearance
CINV	Chemotherapy-Induced Nausea and Vomiting
C_{max}	Maximum Plasma Concentration
CR	Complete response
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CV	Coefficient of variation
DCF	Data Clarification Form
DSMB	Data Safety Monitoring Board
EC	Ethics Committee

ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
ESMO	European Society for Medical Oncology
EU	European Union
F	Oral Bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	Fixed-dose combination
GCP	Good Clinical Practice
h	Hour
HEC	Highly Emetogenic Chemotherapy
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
Ka	Absorption Rate Constant
K2-EDTA	Di-potassium Ethylenediaminetetraacetic acid
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LEC	Low Emetogenic Chemotherapy
LLOQ	Lower limits of quantification
MASCC	Multinational Association of Supportive Care in Cancer
M1,2,3	Metabolites 1,2,3
MEC	Moderately Emetogenic Chemotherapy

NEPA	Netupitant plus Palonosetron
NCCN	National Comprehensive Cancer Network
NK_1	Neurokinin-1
NEPA FDC	Oral Netupitant plus Palonosetron Fixed Dose Combination
NETU	Netupitant
ηi	Individual random effect
OECD	Organisation for Economic Co-operation and Development
OTC	Over The Counter
PALO	Palonosetron
PD	Pharmacodynamic
PE	Physical Examination
PK	Pharmacokinetic
POGO	Pediatric Oncology Group of Ontario
PONV	Post-operative nausea and vomiting
Q/F	Inter-compartmental clearance
QTc	QT Interval Corrected
QTcB	QT Interval Corrected by Heart Rate Using the Bazett formula
QTcF	QT Interval Corrected by Heart Rate Using the Fridericia formula
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBD	To be defined
TEAE	Treatment-Emergent Adverse Event
t_{lag}	Lag Time
t_{max}	Time to reach maximum (peak) plasma concentration following drug administration

$t_{1/2}$	Terminal half-life
TV	Typical values
ULN	Upper limit of normal
US/USA	United States/United States of America
Vd	Apparent Volume of Distribution
Vi/F	Apparent volume of compartment i, i.e., central and peripheral compartment(s), for extravascular administration
WBC	White Blood Cells

1 INTRODUCTION AND RATIONALE

1.1 Background Information

Chemotherapy-induced nausea and vomiting (CINV) is a common and distressing side-effect of cancer chemotherapy regimens in adults, but is also a major problem in the treatment of childhood malignancies. [1, 2, 3]

Adult patients in whom CINV is left uncontrolled, experience a severe deterioration in their quality of life and may experience malnourishment, anxiety, and depression. Fear of CINV is sufficient for many patients to postpone or even refuse potentially life-saving treatment. [3, 4, 5, 6] However, antiemetics can improve quality of life, increase treatment compliance and effectiveness, and therefore improve patient outcome. [7]

Antiemetics counter CINV by antagonising the 5-hydroxytryptamine subtype 3 (5-HT_3) receptor or the neurokinin-1 (NK_1) receptor. Currently, in adult patients undergoing highly emetogenic chemotherapy, the administration of a 5-HT_3 receptor antagonist alongside with a NK_1 receptor antagonist, in association with dexamethasone, is recommended for the treatment of acute CINV. [8, 9]

For patients undergoing a moderately emetogenic chemotherapy regimen, not including a combination of anthracycline plus cyclophosphamide, the 5-HT_3 receptor antagonist palonosetron hydrochloride (Aloxi®) plus dexamethasone is recommended. [9]

In pediatric patients, Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO) guidelines recommend prophylactic antiemetic therapy comprising a 5-HT_3 receptor antagonist and dexamethasone to prevent acute CINV in patients scheduled to receive HEC or MEC. For prevention of delayed CINV, no appropriate studies in children are so far available and therefore no formal recommendation is possible. According to MASCC/ESMO guidelines, however, many panelists suggest that children should be treated in a manner similar to that of adults receiving chemotherapy of this risk, and that doses should be adjusted appropriately for children. [2, 9] The Pediatric Oncology Group of Ontario (POGO) Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients recommend that children scheduled to receive highly emetogenic chemotherapy (HEC) should be administered with antiemetic prophylactic therapy of ondansetron or granisetron plus dexamethasone and aprepitant (≥ 12 years of age and receiving antineoplastic agents not known to interact with aprepitant) or ondansetron or granisetron plus dexamethasone (< 12 years of age or receiving aprepitant interacting agents). For patients scheduled to receive moderately emetogenic chemotherapy (MEC), the recommendation was that patients should receive ondansetron or granisetron plus dexamethasone. [10]

The role of the NK_1 receptor antagonists in children has to be further investigated. It has recently been suggested that the addition of the oral NK_1 receptor antagonist aprepitant to ondansetron with or without dexamethasone may be effective in the prevention of CINV in pediatric patients aged 6 months to 17 years receiving MEC or HEC regimens. [11]

In adults palonosetron hydrochloride administered by the intravenous (IV) and oral routes has a demonstrated efficacy for the management of nausea and vomiting associated with cancer chemotherapy. Its prolonged duration of action offers significant advantages over other 5-HT_3 receptor antagonists. Pharmacological experiments indicate that palonosetron interacts with 5-HT_3 receptors very differently than granisetron or ondansetron and that this differential interaction triggers a receptor alteration or internalization resulting in a long lived inhibition of receptor function. These pharmacological findings may have clinical relevance and contribute to explain the extended antiemetic protection conferred by palonosetron. [12]

In July 2003 the United States (US) Food and Drug Administration (FDA) approved palonosetron 0.25mg IV as a 30-second bolus for the prevention of acute CINV associated with HEC or MEC, and for prevention of delayed CINV associated with MEC (initial and repeat courses) in adults. In Europe, IV palonosetron was approved via the Centralized Procedure in March 2005. Palonosetron is registered in several countries with different trademarks (Aloxi®, Onicit®, Paloxi®). [13]

Safety and efficacy of palonosetron for the prevention of CINV in pediatric population has been so far evaluated in the following clinical studies.

The pediatric study PALO-99-07 [14] evaluated 3 and 10 µg/kg doses of IV palonosetron for preventing highly and moderately emetogenic CINV in the acute phase, in a limited number of pediatric patients (n=35, and n=37, respectively). In the pooled analysis which included randomized and open-label patients, the proportion of patients with a complete response (CR; no emesis and no rescue) during the first 24 h after chemotherapy was higher in the palonosetron 10 µg/kg group than in the 3 µg/kg group (54.1% vs. 37.1%). [14]

The efficacy of two different doses of palonosetron was also tested in pediatric patients undergoing single and repeated cycles of HEC or MEC (PALO-10-20). Overall, the efficacy of palonosetron 20 µg/kg was comparable to that of ondansetron, while the efficacy of palonosetron 10 µg/kg tended to be slightly lower than that of ondansetron. Safety assessments were consistent with the established safety profiles of palonosetron in adults and did not indicate a significant risk to pediatric patients receiving HEC or MEC for up to 4 consecutive cycles. [15]

Palonosetron as intravenous formulation at the dosage of 20 µg/kg (max 1.5 mg) infused over 15 minutes was approved in the US on May 27th, 2014 for pediatric use in patients aged from 1 month to less than 17 years for the prevention of acute nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, including HEC. Similarly, palonosetron intravenous formulation with indication of CINV prevention was extended on February 24th, 2015 in European Economic Area (EEA) to pediatric patients 1 month of age and older.

Helsinn developed an oral fixed-dose combination (FDC) which includes a 5-HT_3 receptor antagonist (palonosetron, 0.5 mg) and an NK_1 receptor antagonist (netupitant, 300 mg) in the form of a hard-gelatine capsule (oral NEPA FDC) to be administered to adults patients as a single administration 1 h prior to chemotherapy.

Netupitant is a new, high-efficient, selective NK_1 receptor antagonist that blocks receptors located in the central nervous system (in the putative vomiting center in the nucleus tractus solitarii) and in the gastrointestinal tract wall (peripheral abdominal vagal afferents). [16]

The oral NEPA FDC has been approved in 2014 in the US for the prevention of acute and delayed nausea and vomiting in adult patients associated with initial and repeated courses of chemotherapy, including but not limited to, HEC, and in the EU for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy and moderately emetogenic cancer chemotherapy. [16]

Oral NEPA FDC (Akynzeo®) is currently officially recommended for MEC and HEC acute and delayed emesis prevention by the National Comprehensive Cancer Network (NCCN) guidelines in adults. [17]

An IV FDC of palonosetron and fosnetupitant is meanwhile under clinical development.

The present study will be a Phase 2 pharmacokinetic/pharmacodynamic (PK/PD) dose finding study of oral netupitant administered concomitantly with oral palonosetron in pediatric cancer patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy. This will be part of the pediatric program of the oral NEPA FDC's line extension, aiming at complying with the post-approval commitments after registration of oral NEPA FDC by FDA.

1.2 Pre-clinical and Clinical Data of Palonosetron

1.2.1 Pre-clinical Data

For a detailed description of pre-clinical data on palonosetron, reference is made to the relevant Investigator's Brochure (IB). [13]

1.2.2 Summary of Phase 1 Clinical Data (Human pharmacokinetics)

Pharmacokinetic in adult subjects

1.2.2.1 Absorption

Following IV administration, an initial decline in palonosetron plasma concentrations is followed by slow elimination from the body with a mean terminal elimination half-life ($t_{1/2}$) of approximately 40 h which is substantially longer than other 5-HT_3 antagonists, i.e., ondansetron (4-6 h), granisetron (5-8 h), tropisetron (7 h) and dolasetron (7 h). Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) are generally dose-proportional over the dose range of 0.3-90 µg/kg in healthy adult subjects and in adult cancer patients.

Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97% mean plasma C_{max} and AUC are generally dose-proportional over the dose range of 0.3-90 µg/kg in healthy subjects and in cancer patients. The mean time to maximum plasma concentration (t_{max}) after oral solution administration was generally 4-6 h. [13]

1.2.2.2 Distribution

Following both oral and IV administrations, palonosetron is widely distributed in the body (volume of distribution of approximately 8.3±2.5 L/kg) and approximately 62% is bound to human-plasma proteins. Age, hepatic dysfunction or mild to moderate renal impairment have no clinically significant effect on the PK of palonosetron although total systemic exposure increases by 28% in patients with severe renal impairment compared with healthy subjects. [13]

1.2.2.3 Metabolism

Palonosetron is eliminated by dual routes; about 40% is eliminated through the kidney and approximately 50% is metabolized to form two primary metabolites: M9 N-oxidepalonosetron (AUC approximately 12% of that of the parent drug) and M4 6-S-hydroxypalonosetron (AUC approximately 3.8% of that of the parent drug). These metabolites have less than 1% of the 5-HT_3 receptor antagonist activity of palonosetron. In vitro metabolism studies have suggested that palonosetron is metabolized primarily by CYP2D6 and to a lesser extent by CYP3A and CYP1A2. Palonosetron does not inhibit or induce cytochrome P450 isoenzymes at clinically relevant concentrations. Metabolite profiling demonstrated that the metabolism of palonosetron following oral administration was consistent with the metabolism following intravenous administration. [13]

1.2.2.4 Elimination

After a single IV dose of 10 µg/kg [^{14}C]-palonosetron, approximately 80% of the dose is recovered within 144 h in the urine, with palonosetron as unchanged active substance representing approximately 40% of the administered dose. After a single IV bolus administration in healthy Caucasian subjects the total body clearance of palonosetron is 173±73 mL/min and renal clearance 53±29 mL/min. The low total body clearance and large volume of distribution result in a terminal elimination half-life of approximately 40 h, which is substantially longer than that of other 5-HT_3 antagonists, i.e., ondansetron (4-6 h), granisetron (5-8 h), tropisetron (7 h) and dolasetron (7 h). Ten percent of patients revealed a mean terminal elimination half-life greater than 100 h. Quantifiable concentrations of palonosetron following oral administration of a single dose (0.75 mg) of radiolabeled [^{14}C]-palonosetron were reported for all subjects until at least 120 h and between 192 and 216 h post-dose in plasma and urine respectively, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in feces. The amount of unchanged palonosetron excreted in the urine represented approximately 40% of the administered dose. In cancer patients, t½ was 48 ± 19 h. After a single-dose of approximately 0.75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 mL/h/kg (mean ± SD) and renal clearance was 66.5 ± 18.2 mL/h/kg. Quantifiable concentrations of M9 metabolite were reported for all subjects until at least 24 h and between 120 and 144 h post-dose in plasma and urine respectively. [13]

Pharmacokinetic in pediatric patients

In pediatric cancer patients (PALO-99-07, [14]), IV administration of 3 and 10 µg/kg palonosetron was characterized by a rapid distribution followed by a slower elimination phase. Exposure, as measured by C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, was generally proportional or slightly less than dose-proportional for the 3 to 10 µ/kg dose levels, across all three evaluated age groups (> 28 days to 23 months, 2 to 11 years, and 12 to 17 years).

Both clearance and volume of distribution appeared to increase with increasing age. These increases were largely due to body weight differences between the three age groups. There were no apparent differences in the distribution of individual patient values across the age groups and doses evaluated. Mean terminal elimination half-life values ranged from 21 to 37 h across the three age groups (individual values ranging from approximately 11 to 81 h) and did not change with dose or age. There was no effect of gender on clearance, volume of distribution or half-life.

In study PALO-10-20 [15], PK parameters of two different IV doses (10 and 20 µg/kg) of palonosetron were determined in pediatric patients undergoing single and repeated cycles of HEC or MEC.

Samples for the PK sub-study were drawn from a total of 95 patients (15 in the < 2 years, 26 in the 2 to < 6 years, 24 in the 6 to < 12 years and 30 in the 12 to < 17 years age group). Of these, 64 patients received palonosetron, while 31 received ondansetron.

After a 15 min infusion, palonosetron PK profiles appear widely comparable for all age groups and both dose levels, with a peak generally reported immediately at the end of infusion, followed by a rapid palonosetron concentration decrease and a much slower elimination phase, with a terminal elimination $t_{½}$ of about 20 to 30 h. A significant difference in $t_{½}$ ($p<0.008$) was observed between age groups with a trend toward longer $t_{½}$ for older patients, although an underestimated determination of $t_{½}$ in patients aged less than 2 years administered with the lowest dose (10 µg/kg) could have influenced the statistical result. Both clearance and volume of distribution appear to increase with increasing age. AUCs values were clearly related to the palonosetron 10 µg/kg and palonosetron 20 µg/kg dose levels. A trend toward increased AUC values (both absolute and nominal dose-adjusted) with age was observed, for which statistical significance was assessed by analysis of variance (ANOVA) for the nominal dose-normalized $AUC_{0-\infty}$ ($p = 0.0027$). No clinically relevant differences were however observed in any of the PK parameters reported between genders or types of chemotherapy. The analyses do not indicate that the PK of palonosetron are strictly dependent on patient age Therefore, no further adjustment of dosing, beyond dosing palonosetron on an individual patient weight basis, is required for pediatric patients.

In conclusion, a PK/PD analysis of the results indicated no clear relationship between drug exposure and response in pediatric patients in the tested IV dose range. None of the patient factors tested, including body weight, age, gender, chemotherapy regimen, or total dose administered, had an impact on the response variables (CR in the acute and the delayed phase).

1.2.3 Clinical Data

Efficacy data in adult patients

In a Phase II study (Study 2330) following HEC, the four highest palonosetron IV doses (3, 10, 30 and 90 µg/kg) were approximately equally effective, with the percentage of patients with CR ranging from 40% to 50% in comparison to the lowest dose cohort (24%; 0.3 to 1 µg/kg). This efficacy profile suggests a plateau in dose response for palonosetron when administered at doses greater than 3 µg/kg (approximately a 0.25 mg fixed dose). Evaluation of the secondary efficacy variables confirmed the clinical efficacy of palonosetron treatment at all tested doses with respect to the lowest dose level. Palonosetron was well tolerated at all dose levels. Adverse events (AEs) were essentially equally distributed across the dose groups, and no dose-related safety relationship was apparent.

Three Phase III studies with IV palonosetron in both moderately and highly emetogenic patient populations (PALO-99-03, PALO-99-04 and PALO-99-05) evaluated doses of 0.25 mg and 0.75 mg (corresponding to 3 µg/kg and 10 µg/kg). These studies demonstrated that the 0.25 mg dose was the lowest effective dose, with no significant difference in safety profile between the doses. In 2003, the 0.25 mg dose was approved for marketing in the US, followed later by registration in several countries worldwide. [13]

Efficacy data in pediatric patients

The study PALO-99-07 [14] evaluated 3 and 10 µg/kg doses of IV palonosetron for preventing highly and moderately emetogenic CINV in the acute phase in the following pediatric age groups: > 28 days to 23 months, 2 to 11 years, and 12 to 17 years of age. Recognizing the overall sample size was limited (n=35, and n=37, respectively), in the pooled analysis which included randomized and open-label patients, the proportion of patients with a CR (no emesis and no rescue) during the first 24 h after chemotherapy was higher in the palonosetron 10 µg/kg group than in the 3 µg/kg group (54.1% vs. 37.1%).

The study PALO-10-20 [15] was a multicenter, active-controlled, double-blind, randomized, parallel group, stratified, double-dummy, Phase 3 study involving 3 study groups receiving palonosetron in two different doses or ondansetron standard therapy for the prevention of CINV. The lower palonosetron dose was 10 µg/kg up to a maximum of 0.75 mg, and the higher palonosetron dose was 20 µg/kg up to a maximum dose of 1.5 mg. The ondansetron dose was 0.15 mg/kg given three times (every 4 h - maximum dose of 32 mg).

The primary objective of this study was to evaluate the efficacy of two different doses of IV palonosetron, compared to ondansetron, in the prevention of CINV in pediatric patients receiving HEC or MEC through 120 h after start of chemotherapy in single and repeated chemotherapy cycles. A total of 494 patients were treated with study drug (167 palonosetron 10 µg/kg, 163 palonosetron 20 µg/kg and 164 ondansetron). Patients were stratified per age group (< 2 years, 2 to < 6 years, 6 to < 12 years and 12 to <17 years) and by emetogenicity (MEC and HEC).

At Cycle 1, the CR in the acute phase of the first study cycle in the Full Analysis Set (FAS) population was reported for 54.2% of patients treated with palonosetron 10 µg/kg, 59.4% of patients treated with palonosetron 20 µg/kg and 58.6% of patients treated with ondansetron. These results indicated an effect of palonosetron 10 µg/kg that was numerically lower, but comparable to that of ondansetron and an effect of palonosetron 20 µg/kg that was numerically similar or comparable to that of ondansetron. Similar results were obtained in the As Treated and Per Protocol populations, with the latter showing a numerically higher effect of palonosetron 20 µg/kg compared to that of the other treatment groups. The study supported the conclusion that palonosetron is non-inferior to ondansetron for the prevention of acute CINV. In patients receiving HEC, CR was the highest in the palonosetron 20 µg/kg group and the lowest in the palonosetron 10 µg/kg in each age group, except in the 2 to < 6 years group where the highest response was shown by palonosetron 10 µg/kg. In the HEC strata, CR rate of palonosetron 20 µg/kg was higher than ondansetron in each age group. In patients receiving MEC, opposite results were observed in the 2 to < 6 years age stratum. In contrast, the CR rate was higher in the ondansetron group than in either palonosetron groups in the 0 to < 2, 6 to < 12 and 12 to < 17 years age strata. For patients receiving HEC, the CR rate in the delayed phase was notably higher in the palonosetron 20 µg/kg group, while for patients receiving MEC the CR rates were comparable across treatment groups.

In line with results observed at Cycle 1, throughout study Cycles 2 to 4, and across all phases, the palonosetron 20 µg/kg treatment group reported in the majority of the cases the highest CR rate, the highest proportions of patients with no vomiting, patients with no emetic episodes and patients with no use of antiemetic rescue medications. Likely due to the progressively lower number of patients, different response rates were reported across the cycles, and statistical significance could not be ascertained for these comparisons as indicated by overlapping 95% CIs.

Safety in adult patients

In adult patients, AEs considered by investigators to be related to palonosetron were consistent with those observed for other 5-HT_3 receptor antagonists as a class or with those expected in a cancer or surgical population, with occasional very minor, non-clinically relevant differences between palonosetron and marketed active comparators [13]. Constipation and headache were the most frequently observed AEs in patients receiving IV or oral palonosetron. These AEs are frequently reported in patients receiving 5-HT_3 receptor antagonists for the prevention of nausea and vomiting associated with cancer chemotherapy or for the prevention of post-operative nausea and vomiting (PONV).

The results of a thorough QT/QTc study (Study PALO-03-11) in adult healthy volunteers demonstrated that palonosetron is not associated with QT prolongation at doses up to 2.25 mg, which provides a 9-fold safety margin for the approved market dose for CINV IV indication, 0.25 mg for adults. [13]

Safety in pediatric patients

As for the pediatric use of palonosetron, its safety has been investigated in two CINV studies (PALO-99-07, PALO-10-20) [14, 15], in children aged between 1 month and

17 years, receiving HEC or MEC, who were administered 3, 10 or 20 µg/kg, up to a maximum total fixed dose of 0.25, 0.75 mg or 1.5 mg, respectively.

The safety profile of palonosetron has been also assessed in two PONV studies (PALO-07-29, PALO-10-14) [18, 19], in pediatric patients aged > 28 days up to 16 years inclusive, undergoing elective surgical procedures requiring general endotracheal inhalation anesthesia, who were administered 1 or 3 µg/kg, up to a maximum total fixed dose of 0.075 or 0.25 mg, respectively.

In these studies, palonosetron was safe and well tolerated at all tested doses, no relevant clinical findings were observed, confirming its safety and efficacy in the prevention of CINV and PONV in pediatric population. [14, 15, 18, 19]

In study PALO-10-20, clinically relevant differences between treatments in the safety profile were not observed in the overall study population or in subgroups of patients based on age, gender, race, ethnicity or emetogenicity of chemotherapy. Safety assessments in this study were consistent with the established safety profiles of palonosetron and ondansetron in adults and did not indicate a significant risk to pediatric patients receiving HEC or MEC for up to 4 consecutive cycles.

Overall, palonosetron was safe and well tolerated at all dosages employed in clinical trials, and no remarkable differences were observed for any safety parameters in both adults and pediatric patients. [13]

For further information about palonosetron, including pharmacokinetics, pharmacodynamics, clinical efficacy and safety, please refer to the current edition of the IB. [13]

1.3 Pre-clinical and Clinical Data of Netupitant

1.3.1 Pre-clinical data

1.3.1.1 Netupitant

A detailed description of the netupitant animal data is provided in the current IB for the oral NEPA FDC. [16]

1.3.2 Summary of Phase 1 Clinical Data (Human pharmacokinetics) of Netupitant

1.3.2.1 Absorption

In single dose oral studies conducted with the administration to healthy volunteers, measurable plasma netupitant concentrations were detected between 45 minutes and 3 h after dosing. Plasma concentrations followed a first order absorption process and reached C_{max} in approximately 5 h. [16]

1.3.2.2 Distribution

The mean apparent volume of distribution (Vd) of netupitant in humans generally ranged from 850 L to over 2000 L, indicating substantial distribution to tissues. The drug is

highly bound to plasma proteins (> 99%) with apparently no large differences in free fraction between healthy subjects and patients with hepatic failure. [16]

1.3.2.3 Metabolism

Netupitant is primarily excreted via hepatic/biliary routes, with renal clearance (CL_R) accounting for less than 5% of CL. Netupitant is metabolized by CYP3A4 to several metabolites. The PK of a single 300 mg dose of netupitant was not affected by co-administration of the CYP3A4 substrates erythromycin (500 mg) or midazolam (7.5 mg). However, netupitant appears to inhibit the metabolism of both these substrates, resulting in an increase in exposure of erythromycin and midazolam proving that netupitant inhibits CYP3A4. Other CYP450 isoenzymes (CYP1A2, CYP2C19, CYP2D6) are not inhibited by netupitant. Netupitant is not an inducer of any CYP450 isoform including CYP2C9. In human liver microsomes, netupitant competitively inhibited the CYP3A4 mediated hydroxylation of testosterone and midazolam (apparent Ki of 1.1 and 2.2 μM, respectively). Therefore, interactions of netupitant with drugs mainly metabolized by CYP3A4, were evaluated in addition to other agents likely to be co-administered with netupitant, in the treatment of highly or moderately emetogenic CINV. [16]

Four metabolites have been identified in human plasma at netupitant doses ≥ 30mg; metabolites M1, M2, and M3 are considered major metabolites. In a human radiolabeled absorption, distribution, metabolism, and excretion (ADME) study on oral netupitant, M1, M2 and M3 accounted for 29%, 14% and 33%, respectively, of total plasma radioactivity exposure (AUC). Exposure for M4 accounted for <10% of the parent. Median t_{max} for metabolite M2 was 5 h and was about 17-32 h for M1 and M3. Oral netupitant, and its 3 major metabolites are extensively bound (> 97%) to plasma protein and all metabolites have been shown to be pharmacologically active. [16]

1.3.2.4 Elimination

The apparent mean elimination half-life of netupitant generally ranged from 30 to approximately 100 h (for oral doses of 30 mg to 450 mg). There was a slightly supra-proportional increase in C_{max} and AUC parameters for doses from 10 mg to 300 mg with dose proportional increases between 300 mg and 450 mg. No trends of CL or Vd changes were seen with increases in dose. [16]

1.3.3 Clinical Data

1.3.3.1 Netupitant Alone or in Combination with Palonosetron

The oral formulation of netupitant, as single agent or in combination with other compounds, including the 5-HT_3 receptor antagonist palonosetron, has been investigated in 27 studies; 20 of them were conducted in healthy adult volunteers. A total of 1,939 adult subjects and patients received netupitant in combination with palonosetron and 206 adult subjects and patients received oral netupitant alone.

Oral netupitant was generally well tolerated at all dose levels tested. In healthy volunteers, the most frequently reported treatment-emergent adverse events (TEAEs) related to netupitant alone (not in combination) were headache, fatigue, somnolence,

nausea, asthenia, lethargy, diarrhea and abdominal pain. In phase 2 and phase 3 studies in cancer patients, the oral NEPA FDC showed a good safety profile and proved to be effective for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of MEC and HEC. [16]

In the Phase 2 and Phase 3 studies, leading to oral NEPA FDC (Akynzeo®) approval, the type, frequency and intensity of AEs were comparable across treatment groups. There was no apparent dose-response effect and the safety profile of the oral NEPA FDC was similar to that of other dose combinations, to that of palonosetron alone and to that of aprepitant in combination with ondansetron or palonosetron (comparators in the Phase 2 and 3 studies). There were no clinically significant changes in laboratory parameters. No clinically significant changes in vital signs were reported across all studies. All data regarding electrocardiograms (ECGs) and QT intervals suggest no clinically relevant effects for QT prolongation in the Phase 1, Phase 2 and Phase 3 studies and in a thorough QTc study.

Further details are provided in the current IB of oral NEPA FDC. [16]

Pediatric studies have not been performed so far on the netupitant alone, or as a component in combination such as Akynzeo®.

1.4 Study Rationale

This study (NEPA-15-31) will be a Phase 2 PK/PD dose-finding study of oral netupitant administered concomitantly with oral palonosetron in pediatric cancer patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy. This will be part of the pediatric program of the oral NEPA FDC's line extension, aiming at complying with the post-approval commitments after registration of oral NEPA FDC (Akynzeo®) by US FDA.

The selection of the netupitant doses to be used in this study is supported by efficacy and safety data in adults from Akynzeo® pivotal studies NETU-07-07 (HEC) [20] and NETU-08-18 (MEC) [21]. In those studies, the efficacy and safety of oral netupitant doses of 100, 200 and 300 mg (NETU-07-07 [20]) and 300 mg (NETU-08-18 [21] and NETU-10-29 [22]) in combination with oral palonosetron (0.5 mg) were assessed.

During the development of oral Akynzeo®, netupitant doses of 100, 200, 300 and 450 mg have been tested in the adult population (see studies NP16601, NP16603, NETU-06-27, NETU-06-07, NETU-07-01, NETU-10-29). All doses proved to be well tolerated and doses of 100 and 300 mg showed antiemetic efficacy in pivotal clinical trials in cancer patients undergoing emetogenic chemotherapy treatments. [16, 20, 21, 22]

In this study (NEPA-15-31), the following two different netupitant dosages will be tested in patients aged from 3 months to < 18 years: 1.33 mg/kg up to a maximum of 100 mg, and 4 mg/kg up to a maximum of 300 mg. Because netupitant elimination is mainly mediated by CYP3A4 metabolism, due to CYP3A4 ontogeny (where CYP3A4 capacity in 12 month olds is about 40% of adult levels), the youngest patient age classes (< 3 months of age) will be treated at lower doses: i.e., 0.8 mg/kg and 2.4 mg/kg. All

netupitant doses in all age classes will be concomitantly administered with palonosetron 20 µg/kg (up to a maximum dose of 1.5 mg).

Study NEPA-15-31 is planned to be the first pediatric clinical trial involving netupitant, together with oral palonosetron. A single oral palonosetron dose of 20 µg/kg (up to a maximum dose of 1.5 mg) will be used in this study. This corresponds to the IV palonosetron dose approved by USA FDA for the pediatric population. The approval was based on efficacy and safety data from IV palonosetron study PALO-10-20 [15] in pediatric patients (HEC/MEC) aged 1 month to < 17 years. Since the absolute bioavailability of oral palonosetron is approximately 97% in adult subjects (as stated in IV Aloxi® labeling), similar safety and efficacy as demonstrated in PALO-10-20 [15] is expected in NEPA-15-31 from the 20 µg/kg palonosetron component given as an oral solution.

The role of corticosteroids in concomitance with 5-HT_3 and NK_1 receptor antagonists to prevent CINV is controversial and less well established in pediatric cancer patients when compared to adults, partially because they are commonly used in pediatric population as part of chemotherapy regimens. [2]

Overall, a number of common pediatric chemotherapy regimens include a corticosteroid, usually prednisone or dexamethasone, as an essential component of chemotherapy. [2] Netupitant is expected to increase systemic exposure to dexamethasone and prednisone. [23]

Moreover, due to the interaction, pediatric oncologists may decide not to use netupitant in pediatric cancer patients receiving dexamethasone or prednisone as part of their chemotherapy. The same safety concerns are true for other clinical trials with any NK_1 receptor antagonist given with steroids, and these were also reported in previous pediatric CINV trials with aprepitant. [11]

The Sponsor has concerns to safely enroll a “broader” population involving pediatric patients receiving systemic corticosteroids as part of their chemotherapy regimen, even though it is recognized that these safety considerations may reduce the pool of pediatric cancer patients available to enroll in NEPA-15-31.

Therefore, any pediatric patients receiving systemic corticosteroid therapy started within 72 h prior to study drug administration and/or scheduled to receive a corticosteroid as part of their chemotherapy regimen during the study should not be eligible for this study since there are too many risks and unknowns.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective is to investigate the PK/PD correlation between netupitant exposure and antiemetic efficacy after a single oral netupitant administration, concomitantly with oral palonosetron in pediatric cancer patients receiving MEC or HEC treatments. Efficacy parameter to be used in the correlation is the proportion of patients with CR (i.e., no emetic episodes and no rescue medication) during the delayed phase (> 24-120 h after the start of chemotherapy on Day 1).

2.2 Secondary

The secondary objectives are the following:

- to assess the safety and tolerability after single oral administration of netupitant given concomitantly with a single oral administration of palonosetron;
- to evaluate the PK profile of oral palonosetron at the fixed dose of 20 µg/kg in pediatric patients with the concomitant administration of netupitant.

3 STUDY PLAN

3.1 Study Design

This is a multicenter, multinational, randomized, double-blind, stratified (by age class; by emetogenicity; by chemotherapy schedule), dose-finding, Phase 2 study involving two treatment groups receiving a single oral dose of netupitant administered concomitantly with oral palonosetron.

The study is planned to be performed at a minimum of approximately 16 sites in USA, Russia, Ukraine and Serbia; more sites and/or countries may be added if necessary.

A total of 92 pediatric cancer patients receiving either HEC or MEC will be enrolled in the study.

The patients will be enrolled into one of two netupitant dose treatment groups (46 patients/group):

- Treatment group 1: from 1.33 mg/kg up to a maximum of 100 mg (for patients < 3 months of age the netupitant dose will be 0.8 mg/kg)
- Treatment group 2: from 4 mg/kg up to a maximum of 300 mg (for patients < 3 months of age the netupitant dose will be 2.4 mg/kg)

Each netupitant dose is administered with 20 µg/kg palonosetron (up to a maximum of 1.5 mg).

The study will be stratified by the following criteria:

- Age class:
  - Birth to < 1 month
  - 1 to < 3 months
  - 3 to < 6 months
  - 6 to < 12 months
  - 1 to < 2 years
  - 2 to < 5 years
  - 5 to < 12 years
  - 12 to < 18 years
- Emetogenicity:
  - HEC
  - MEC
- Chemotherapy schedule:
  - HEC/MEC on Day 1 only
  - HEC/MEC on multiple days

Within each stratum, patients will be randomized prior to study drug administration to one of the two previously mentioned netupitant treatment groups.

An exception will be the younger age classes (all age classes < 12 months) for which the safety of the lowest netupitant dose(s) will be evaluated before escalating to the subsequent netupitant dose groups. For these age classes the Emetogenicity and Chemotherapy schedule strata will not be considered, even not when randomization will start in relevant class.

The treatment plan is described in detail here below and is summarized in Appendix 1.

At the beginning of the study enrolment is open only to:

- patients aged ≥ 1 year, who will be randomized to one of the two netupitant doses
- patients aged 6 months to < 12 months who will be treated with the netupitant lower dose (1.33 mg/kg)

At the beginning of the study three patients aged **6 to < 12 months** will be first enrolled in the lower netupitant dose group (1.33 mg/kg). As soon as these first 3 patients have completed the study, without safety and tolerability concerns as assessed by Data Safety Monitoring Board (DSMB), enrolment in the higher netupitant dose group (4 mg/kg) of the same age class (6 to < 12 months) can start.

As soon as 6 patients in the age class 6 to < 12 months (3 patients for each netupitant dose group) have completed the study without safety and tolerability concerns, decision by DSMB will have to be taken whether a) all remaining patients 6 to <12 months can be randomized to one of the two netupitant treatment doses and start the assigned treatment, and b) the lower age class **3 to < 6 months** may start the treatment with the lower dose.

The enrollment of the remaining cohorts will occur in parallel keeping the original treatment dose escalation scheme: 3 patients will be first treated with the lower netupitant dose. As soon as these first 3 patients will have completed the study and no safety and tolerability concerns are shown, as assessed by the DSMB, enrolment in the higher dose group in the same age class will start [37].

3.2 Study Duration

The planned duration of the study is a maximum of 31 days for each patient, which includes screening up to 14 days before randomization (up to 7 days for patients aged < 2 years), day of enrolment/randomization, administration of study drugs and chemotherapy (Study Day 1), and the PK visit (Study Days 2 to 5). The final visit will be 6, 7 or 8 days after study drug administration, and a follow up visit / telephone contact will be performed between 14 and 17 days after study drug administration.

3.3 Study Population

Male and female pediatric cancer patients from birth up to < 18 years, scheduled to receive HEC or MEC to be administered as single day chemotherapy on Day 1 only or for multiple days.

3.3.1 Number of Patients

The number of patients to be treated is estimated to be 92, distributed in two treatment groups (i.e., 46 patients/group). For each age class included in the stratification, the relevant planned number of patients to be enrolled is provided below. For the sample size calculation please refer to Section 8.1 Sample Size Determination.

Age classes	Number of patients to be included
Birth to < 1 month	12
1 to < 3 months	12
3 to < 6 months	8
6 to < 12 months	8
1 to < 2 years	8
2 to < 5 years	12
5 to < 12 years	16
12 to < 18 years	16
Overall	***92***

3.3.2 Inclusion Criteria

Patients must meet the following criteria to be eligible to participate in the study:

1. Signed written informed consent by parent(s)/legal guardians of the pediatric patient in compliance with the local laws and regulations. In addition signed children's assent form according to local requirements.
2. Male or female in- or out-patient from birth to < 18 years at the time of randomization.
3. Patient weight at least 3.3 kg.
4. Naïve or non-naïve patient with histologically, and/or cytologically (or imaging in the case of brain tumors or nephroblastoma) confirmed malignant disease.
5. Scheduled and eligible to receive at least one moderately or highly emetogenic chemotherapeutic agent on Day 1 only or for multiple days (Appendix 2).
6. For patient aged ≥ 10 years: Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2 (Appendix 3).
7. Adequate hepatic function defined as serum ALT and AST ≤ 2.5 ULN, and total bilirubin ≤ 1.5 ULN.
8. Adequate renal function defined as estimated glomerular filtration rate (eGFR) ≥ 70 ml/min/1.73m^2 (≥ 50 ml/min/1.73m^2 for children < 3 months old). The eGFR should be calculated using the modified Schwartz equation (Appendix 5).
9. For patient with known history or predisposition to cardiac abnormalities: in the Investigator's opinion the history/predisposition should not jeopardize patient's safety during the study.

10. If the patient is female, she shall: a) not have attained menarche yet or b) have attained menarche and have a negative pregnancy test at the screening visit and at Day 1.
11. Male or female fertile patient using reliable contraceptive measures (such measures, for patient and sexual partner, include: implants, injectables, combined oral contraceptives, intrauterine devices, vasectomized/sterilized partner, use of a double-barrier method or sexual abstinence). The patient and his/her parent(s)/legal guardians must be counseled on the importance of avoiding pregnancy before or during the study.

All inclusion criteria will be checked at screening visit (Visit 1). Inclusion criteria #3, 5, 10 will be re-checked at Day 1 (Visit 2).

Local laboratory results from an appropriately certified local laboratory could be used at the discretion of Investigator to evaluate patients' eligibility.

3.3.3 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible for admission into the study:

1. The patient and/or parents/caregivers are expected by the Investigator to be non-compliant with the study procedures.
2. Patient has received or is scheduled to receive total body irradiation, total nodal irradiation, upper abdomen radiotherapy, half or upper body irradiation, radiotherapy of the cranium, craniospinal regions, head and neck, lower thorax region or the pelvis within 1 week prior to study entry (Day 1) or within 120 h after start of chemotherapy administration on Day 1.
3. Known history of allergy to any component or other contraindications to any NK_1 or 5-HT_3 receptor antagonists.
4. Active infection.
5. Any illness or condition that, in the opinion of the Investigator, may pose unwarranted risks in administering the investigational product to the patient.
6. Patient suffering from ongoing vomiting from any organic etiology (including patients with history of gastric outlet obstruction or intestinal obstruction due to adhesions or volvulus, patients with a symptomatic CNS tumor causing nausea and/or vomiting) or patient with hydrocephalus.
7. Patient who experienced any vomiting, retching, or nausea within 24 h prior to the administration of the study drug (note: functional vomiting for infants, which is normally seen during the first 3 months of life, is not to be considered as vomiting).
8. Patient who received any drug with potential anti-emetic effect within 24 h prior to the start of reference chemotherapy, including but not limited to:
   - NK_1- receptor antagonists (e.g., aprepitant or any other new drug of this class);
   - 5-HT_3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron, tropisetron, ramosetron);
   - Benzamides (e.g., metoclopramide, alizapride);
   - Phenothiazines (e.g., prochlorperazine, promethazine, perphenazine, fluphenazine, chlorpromazine, theithylperazine);

- Benzodiazepines initiated 48 h prior to study drug administration or expected to be received within 120 h following initiation of chemotherapy, except for single doses of midazolam, temazepam or triazolam;
- Butyrophenones (e.g., droperidol, haloperidol);
- Anticholinergics (e.g., scopolamine, with the exception of inhaled anticholinergics for respiratory disorders, e.g., ipratropium bromide);
- Antihistamines (e.g., diphenhydramine, cyclizine, hydroxyzine, chlorphenhyramine, dimenhydrinate, meclizine);
- Domperidone;
- Mirtazapine;
- Olanzapine ;
- Prescribed cannabinoides (e.g., tetrahydrocannabinol, nabilone);
- Over the Counter (OTC) antiemetics, OTC cold or OTC allergy medications;
- Herbal preparations containing ephedra or ginger.

9. Patient who received palonosetron within 1 week prior to administration of study drug.
10. Patient who has been started on systemic corticosteroid therapy within 72 h prior to study drug administration or is planned to receive a corticosteroid as part of the chemotherapy regimen.
    Exceptions:
    - Patient who is receiving chronic (> 72 h), daily steroid therapy can be enrolled provided the steroid dose is not > 0.14 mg/kg (up to 10 mg) of prednisone daily or equivalent.
    - For supportive care, patient is permitted to receive a single dose of corticosteroid during the 72 h prior to study drug administration (but not < 12 h prior to study drug administration) provided it is less than the equivalent of 20 mg of prednisone.
11. Patient aged < 6 years who received any investigational drug (defined as a medication with no marketing authorization granted for any age class and any indication) within 90 days prior to Day 1, or patient aged ≥ 6 years who received any investigational drug within 30 days prior to Day 1 or is expected to receive investigational drugs prior to study completion.
12. Intake of alcohol, food or beverages (e.g., grapefruit, cranberry, pomegranate and aloe vera juices, German chamomile) known to interfere with either CYP3A4 or CYP2D6 metabolic enzymes within 1 week prior to Day 1 and during the overall study period (Appendix 4).
13. Use of any drugs or substances known to be strong or moderate inhibitors of CYP3A4 and CYP2D6 enzymes within 1 week prior to Day 1 or planned to be used during the overall study period (Appendix 4).
14. Use of any drugs or substances known to be CYP3A4 substrates with narrow therapeutic range within 1 week prior to Day 1, or planned to be used during the overall study period (Appendix 4).
15. Use of any drugs or substances known to be inducers of CYP3A4 enzymes within 4 weeks prior to Day 1 or planned to be used during the overall study period (Appendix 4).

16. Lactating female patient.
17. Patient with clinically relevant Grade 3 or 4 non-hematological abnormal laboratory values.
20. Enrolment in a previous study with netupitant (either alone or in combination with palonosetron).
21. Marked baseline prolongation of QTc interval [QTcB or QTcF > 460 msec] at screening.

NOTE: Exclusion criteria ## 18 and 19 were skipped intentionally to maintain consistency in exclusion criteria numbering between protocol amendments.

All exclusion criteria will be checked at screening visit (Visit 1). Exclusion criteria #2, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 17, 21 will be re-checked at Day 1 (Visit 2). In case of ERT central ECG report pending, the assessment of compliance with exclusion criterion #21 could be made based on automatic interpretation of QTcB and QTcF results by ECG machine at the discretion of Investigator.

All eligible patients must be approved for randomization by authorized Medical Monitor.

4 STUDY DRUG MANAGEMENT

4.1 Description of Investigational Medicinal Products

The following investigational medicinal products (IMPs) will be used during the study:

Name:	**Oral Netupitant (IMP 1)**
Dosage form:	glass vial with liquid formulation (suspension)
Strength:	100 mg netupitant / 7 mL
Dosing:	netupitant will be administered based on the body weight as a single oral dose 1 h (± 10 minutes) prior to start of emetogenic chemotherapy on Day 1
Route of administration:	oral

Name:	**Oral Netupitant (IMP 2)**
Dosage form:	glass vial with liquid formulation (suspension)
Strength:	300 mg netupitant / 7 mL
Dosing:	netupitant will be administered based on the body weight as a single oral dose 1 h (± 10 minutes) prior to start of emetogenic chemotherapy on Day 1
Route of administration:	oral

Name:	**Oral Palonosetron (IMP 3)**
Dosage form:	glass vial with liquid formulation (solution)
Strength:	0.75 mg palonosetron / 5 mL (oral administration of the 0.75 mg/5 mL solution for IV use)
Dosing:	palonosetron will be administered based on the body weight at the dosage of 20 µg/kg (max 1.5 mg), immediately (within 5 minutes) after netupitant, i.e., 1 h (± 10 minutes) prior to start of emetogenic chemotherapy on Day 1
Route of administration:	oral

4.2 Treatment Groups

A total of 92 pediatric cancer patients will be enrolled to one of two treatment groups (46 patients/group):

- **Treatment group 1** – patients ≥ 3 months of age will receive a single oral netupitant dose of 1.33 mg/kg (up to a maximum of 100 mg for patients weighting 75 kg or more) concomitantly with a single oral palonosetron dose of 20 µg/kg (up to a maximum of 1.5 mg for patients weighting 75 kg or more). For patients < 3 months of age, the netupitant dose will be 0.8 mg/kg.
- **Treatment group 2** – patients ≥ 3 months of age will receive a single oral netupitant dose of 4 mg/kg (up to a maximum of 300 mg for patients weighting 75 kg or more) concomitantly with a single oral palonosetron dose of 20 µg/kg (up to a maximum of 1.5 mg for patients weighting 75 kg or more). For patients < 3 months of age, the netupitant dose will be 2.4 mg/kg.

4.3 Dose and Administration

The netupitant doses to be tested in the pediatric population will match exposures to adult doses of 100 up to 300 mg as tested in pivotal Phase 2 trial NETU-07-07 [20], and 300 mg as tested in pivotal Phase 3 trials (NETU-08-08 [21] and NETU-10-29 [22]. These doses proved to be safe and effective. Basic assumption behind this choice is that efficacious netupitant AUC values in children are similar to those observed in adults at effective doses.

In order to predict the pediatric doses matching exposures to adult doses of 100 and 300, CL/F values in different age classes were estimated by pharmacokinetic allometry scaling according to the following model:

$$(\mathrm{CL/F})\mathrm{p} = (\mathrm{CL/F})\mathrm{a} * \left(\frac{\mathrm{BWp}}{70}\right)^{\mathrm{ADE}}$$

where (CL/F)p and (CL/F)a are the systemic clearances in pediatric patients and adults, respectively, BWp is the body weight of children, 70 is the standard adult BW expressed in kg, and ADE is an age-dependent exponent [24]. ADE values across the age classes were assumed to be the following [24]: 1.2 for children aged ≤ 3 months, 1.0 for those aged > 3 months to 2 years, 0.9 for those aged > 2 years to 5 years, and 0.75 for those aged > 5 years. The model accounts for the effect of the body size change and organ maturation. An age-dependent exponent that decreases with the age increase, is consistent with a faster functional maturation occurring during the youngest age ranges.

Reference body weights for children were taken from growth charts compiled by the CDC (Centers for Disease Control and Prevention, Atlanta, GA, USA) [25].

Average AUC values in adults receiving 100 and 300 netupitant have been calculated by dividing these doses by the geometric mean of netupitant clearance in adults, (CL/F)a = 20.27 L/h, obtained from the population PK study (Study NETU-10-02 [26]), assuming linear kinetics. The netupitant doses for each pediatric age classes that are expected to yield these target AUC values have been calculated by multiplying AUCs by

the respective predicted CL/F in children, assuming the same netupitant oral bioavailability (F) in pediatric patients and adults.

In conclusion, netupitant doses per age class to be tested in the PK/PD-based dose finding study in pediatric patients resulted to be the following:

Age class	Dose 1 (mg/kg)	Dose 2 (mg/kg)
Birth to < 1 month	0.8	2.4
1 month to < 3 months	0.8	2.4
3 months to < 6 months	1.33	4
6 months to < 12 months	1.33	4
1 year to < 2 years	1.33	4
2 years to < 5 years	1.33	4
5 years to < 12 years	1.33	4
12 years to < 18 years	1.33	4
ADULTS and children with BW ≥ 75 kg	100 mg	300 mg

Patients enrolled in each of the two treatment groups will receive a single oral dose of netupitant per kg body weight as described in Section 4.2 Treatment Groups, 1 h (± 10 minutes) prior to start of emetogenic (HEC or MEC) chemotherapy on Day 1 and a single oral dose of palonosetron at the dosage of 20 µg/kg (maximum 1.5 mg), immediately (within 5 minutes) after netupitant, i.e., 1 h (± 10 minutes) prior to start of emetogenic (HEC or MEC) chemotherapy on Day 1.

4.4 Packaging and Shipment

The investigational products (netupitant vials and palonosetron vials) will be provided in sealed and appropriately labeled study kits. The netupitant vials included in the kits will have the same appearance for all the dosages; the different concentrations of the active pharmaceutical ingredient (API) permit to have different netupitant dosages by using the same volume, which is weight-based defined.

Packaging and labeling of the study drugs will be carried out in accordance with all applicable regulatory/legal requirements by CSM Europe SA (previously B&C Group) (Belgium).

Study kit is inside of a carton box and contains 2 vials of palonosetron (up to 1.5 mg dosage), 1 vial netupitant suspension and the ancillaries to be used for the collection and administration of the drugs. All the components of the study kits are identifiable with differently colored labels.

The procedure to be followed for the preparation and administration of the drugs will be included in the Drug Manual provided to the site staff before the start of the study (also refer Section 4.8 Randomization, Blinding and Assignment of Study Drug).

The study kits will be delivered either to a designated person at the site's Pharmacy or directly to the Investigator or designated staff, as applicable.

4.5 Storage

The study drug will be delivered and stored at room temperature (below 25°C), in a secure area with limited access and protected from direct light. At the study site, the designated responsible person for storage of the investigational product (the site pharmacist or the Investigator or a designee) should also make sure that the drugs are kept separately from the other medications available on site and in no circumstance should be mixed up with any other medications used at the trial site.

4.6 Drug Depots

The study drugs kits will be shipped from the central depot to either local drug depots, or directly to the study sites, as applicable.

4.7 Accountability

Once the kits are received at the study site, the pharmacist or designated responsible person will sign a drug receipt form. Adequate records of the receipt, dispensation and return of study drugs must be maintained throughout the study. Used study drug kits will be retained until the drug accountability has been checked by a designated monitor; a peel-off portion of the study drug label will also be affixed to the drug preparation form as an additional accountability measure in case internal policies require immediate disposal of the vials. Unused study drug kits remaining at investigational sites at the end of the study will be returned to the drug depots for destruction or will be destroyed at the sites as applicable. At the end of the study, delivery records will have to be reconciled with those of used and returned stocks. Any discrepancy will have to be accounted for. Destruction of unused medication will be documented in writing according to FDA IND regulation 21CFR312.59, ICH Good Clinical Practice (GCP) and the drug depot Standard Operating Procedures (SOPs). Any destruction of remaining study drugs material is to be first approved in writing by the study Sponsor.

4.8 Randomization, Blinding and Assignment of Study Drug

Randomization will be used to avoid bias in assigning patients to treatment and to increase the likelihood that known and unknown patient attributes are evenly balanced across treatment groups.

A computer-generated list of the kit numbers ("packaging list") will be prepared by the Contract Research Organization (CRO) to allow for blinding of the two treatment groups. Sealed cartons (kits) containing the study drugs will be prepared according to this packaging list. An appropriate amount of treatment kits will be supplied to the designated person at the investigational sites at the beginning of the study, with further re-supplies scheduled once the number of available treatment kits decrease to a pre-set threshold at each site. Kits are indistinguishable, i.e., the netupitant vials contained in the kits have the same appearance for all the dosages; the different concentrations of the API permit to

have different netupitant dosages by using the same volume, which is weight-based defined.

The computer-generated patient randomization list(s) will be prepared by the CRO to allow for random treatment allocation where/when a random treatment allocation is foreseen. The Interactive Web Response System (IWRS) provider and a designated person at Helsinn will retain master copies of the packaging and patient randomization lists in a secure fashion to maintain the blind.

Sponsor project team members and members of the Investigator's team will not have access to the lists. Patients will enter the study according to the design described in Section 3.1 Study Design and in Appendix 1.

Randomization/treatment assignment of eligible patients will be done using IWRS integrated with EDC system. Patients will be registered in the EDC at screening visit, and patient identification number will be automatically assigned by the system. Once a patient fulfills the inclusion and exclusion criteria, at Day 1 (Visit 2) the Investigator will ask for randomization/treatment assignment through the EDC. The patient's date of birth, the emetogenicity and the schedule of the chemotherapy (all the information is necessary for identifying the patient's strata) and the body weight (necessary to establish the total dosages of netupitant and palonosetron to be administered) are taken into consideration. These and other demographic data are stored in the IWRS module, together with the assigned treatment.

The IWRS will assign the treatment to be administered to the patient through a static central blocked randomization for patients to be randomized and treated in a double-blind fashion. The IWRS will assign the treatment to be administered to the patient in the youngest age classes (all age classes < 12 months) according to the study design, i.e. the lowest netupitant dose(s) will be assigned and evaluated before escalating to the subsequent netupitant dose groups.

Using the assigned dosage and the patient's weight, IWRS will customize patient-specific instructions for study drug preparation and send them to designated person at the study site.

The designated person at site will prepare the study drug following the instructions provided by the IWRS.

The IWRS will be open for randomization / treatment assignment only for the age-class(es) that are allowed to include patients, according to the design and to the DSMB decisions. The IWRS will be closed for each age class once the relevant number of enrolled patients reached the planned target number of patients.

4.8.1 Emergency Unblinding Procedure

As all patients will be treated with netupitant, it is unlikely that knowledge of the specific doses administered to an individual patient will provide sufficient additional information to the Investigator to warrant breaking the blind for the patient.

However, if the Investigator considers it essential to know the dose of netupitant administered in order to adequately respond to a medical emergency, the Investigator can obtain the treatment assignment of an individual patient through the IWRS. If possible, the Investigator should discuss with the CRO Medical Monitor whether unblinding is essential prior to contacting IWRS for the unblinding of the patient's treatment assignment.

In case of unblinding, the Sponsor and CRO will be notified in a blinded fashion immediately through an automatic communication of the IWRS. Moreover, the Investigator should notify the CRO Medical Monitor and the Sponsor Drug Safety within 24 h of the performed emergency unblinding.

If the blind is broken for an individual patient, the Investigator must record the following information in the patient's source documents:

- The date and time the blind was broken.
- The reason the blind was broken.

In case of unblinding by the Investigator, the patient will be withdrawn from the study.

If the blind is broken by the Sponsor (via IWRS) for pharmacovigilance reporting purposes in case of a suspected unexpected serious adverse reaction (SUSAR), the blind will be maintained for all other persons involved in this study. The patient will not be withdrawn from the study in case of unblinding by the Sponsor's Drug Safety Unit for pharmacovigilance reporting purposes.

Any unblinding will be performed through IWRS (24-h coverage), and the unblinding procedure is described in detail in the IWRS instruction manual that will be provided separately. For the DSMB the unblinding process is described in the DSMB charter.

4.9 Over-dosage

In the unlikely event of overdose, the patient should be managed with supportive care. In case of symptomatic overdose, conservative management of signs and symptoms is advised. No case of over-dosage has been reported with netupitant or palonosetron to date. No antidote for palonosetron or netupitant overdose is known.

4.10 Prior and Concomitant Medications

Information on prior and concomitant medications will be collected beginning 14 days prior to Day 1 up to the follow-up visit (Day 14 [+3]).

4.10.1 Prior and Concomitant Treatments for the Prevention of Nausea and Vomiting or with Potential Antiemetic Effect

The use of any medication for the prevention of nausea and vomiting or the use of any medication with potential antiemetic effects within the 24 h prior to the start of emetogenic chemotherapy or during the 120 h after the start of emetogenic chemotherapy is prohibited. For patients undergoing multiday emetogenic chemotherapy, preventive antiemetic medication can be administered starting from > 24 h after start of emetogenic chemotherapy (HEC or MEC) on Day 1. The antiemetic treatment shall be administered

as per local practice; however any further administration of netupitant or palonosetron is prohibited.

The list of prohibited medications includes, but is not limited to:

- NK1- receptor antagonists (e.g., aprepitant or any other new drug of this class);
- 5-HT3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron, tropisetron, ramosetron);
- Benzamides (e.g., metoclopramide, alizapride);
- Phenothiazines (e.g., prochlorperazine, promethazine, perphenazine, fluphenazine, chlorpromazine, theithylperazine);
- Benzodiazepines initiated 48 h prior to study drug administration or expected to be received within 120 h following initiation of chemotherapy, except for single doses of midazolam, temazepam or triazolam;
- Butyrophenones (e.g., droperidol, haloperidol);
- Anticholinergics (e.g., scopolamine, with the exception of inhaled anticholinergics for respiratory disorders e.g., ipratropium bromide);
- Antihistamines (e.g., diphenhydramine, cyclizine, hydroxyzine, chlorphenhyramine, dimenhydrinate, meclizine);
- Domperidone;
- Mirtazapine;
- Olanzapine;
- Prescribed cannabinoides (e.g., tetrahydrocannabinol, nabilone);
- Over the Counter (OTC) antiemetics, OTC cold or OTC allergy medications;
- Herbal preparations containing ephedra or ginger.

The intake of palonosetron is not permitted within 1 week prior to administration of study drug.

The start of any systemic corticosteroid therapy within 72 h prior to study drug administration or the administration of a corticosteroid as part of the chemotherapy regimen is not permitted.

The following exceptions are allowed:

- Patients who are receiving chronic (> 72 h), daily steroid therapy can be enrolled, provided the steroid dose is not > 0.14 mg/kg (up to 10 mg) of prednisone daily or equivalent.
- For supportive care, patients will be permitted to receive a single dose of corticosteroid during the 72 h prior to study drug administration (but not < 12 h prior to study drug administration) provided it is less than the equivalent of 20 mg of prednisone.

Rescue medication for treatment of nausea and vomiting is permitted after the start of emetogenic chemotherapy administration; however any further administration of netupitant or palonosetron is prohibited; use of metoclopramide is not permitted as rescue medication (see Section 4.11 Rescue Medication).

4.10.2 Prior and Concomitant Cancer Chemotherapy and Radiotherapy

Patients must be scheduled to receive a course of HEC or MEC, administered on Day 1 only or on multiple Days, either alone or in combination with other chemotherapeutic agents (see Appendix 2). For consistency of interpretation, "multiple days" schedule would include regimens with additional HEC/MEC given between Day 1 and Day 6 (within 120 hours from the start of first HEC/MEC administration on Day 1).

Any low emetogenic chemotherapy (LEC) agent or minimally emetogenic agent given, as part of the aforementioned chemotherapy regimens using HEC or MEC, is allowed at any time during the study and does not have any impact on the time of study drugs administration.

Total body irradiation, total nodal irradiation, upper abdomen radiotherapy, half or upper body irradiation, radiotherapy of the cranium, craniospinal regions, head and neck, lower thorax region or the pelvis within 1 week prior to study entry (Day 1) or within 120 h after study drug administration on Day 1 are not permitted.

4.10.3 Other Prior and Concomitant Medications

All medications used within 14 days prior to Day 1, or administered during the study as clinically indicated, are to be recorded on the appropriate electronic case report form (eCRF) pages. Prophylactic infusion of saline solution in order to prevent toxic reactions related to chemotherapy is to be recorded. Infusion of blood products has to be recorded. All medications administered in relation to diagnostic procedures (e.g., anesthetics, or antibiotics) are to be recorded.

According to protocol exclusion criterion #11, any investigational drug taken within 90 days prior to Day 1 for patients aged < 6 years, or any investigational drug within 30 days prior to Day 1 for patients aged ≥ 6 years, or through the entire study period are not allowed. For this purpose "Any investigational drug" has to be intended as a medication with no marketing authorization granted for any age class and any indication.

Based on exclusion criteria #13 and 14, the intake of any drugs or substances known to be strong or moderate inhibitors of CYP3A4 and CYP2D6 enzymes, including any of the narrow therapeutic range CYP3A4 substrates, within 1 week prior to Day 1 or use of such medications during the overall study period (until Visit 5 inclusive) is not permitted (Appendix 4).

Based on exclusion criterion #15, the intake of drugs or substances known to be inducers of CYP3A4 enzymes within 4 weeks prior to the dosing day or use of such medications during the overall study period (until Visit 5 inclusive) is not permitted (Appendix 4).

4.11 Rescue Medication

Rescue medication should be administered to alleviate established, refractory or persistent nausea or vomiting and will be permitted on an as-needed basis.

Anti-emetic medications are not allowed as prevention of emesis, nor to increase the expected antiemetic effects of the study drugs, except for patients receiving HEC or MEC beyond Day 1.

Rescue medication is defined as any medication taken to alleviate nausea or vomiting (i.e., with indication nausea or vomiting) during the period from start of emetogenic chemotherapy to 120 h later. The choice of rescue medication will be at the discretion of the Investigator. Investigator must ensure that rescue medication is made available to patients whenever needed.

Use of palonosetron or netupitant other than study drugs administration is not permitted.

Use of metoclopramide is not permitted as rescue medication.

5 STUDY CONDUCT

5.1 General Instructions

During the course of the study, patients will undergo the following visits (see also the Flow chart):

- Visit 1, screening (Day -14 to -1 or Day -7 to -1 for patients aged < 2 year), during which patients will be assessed for eligibility.
- Visit 2 (Day 1), during which patients fulfilling eligibility criteria will be enrolled, randomized (as applicable), administered study drugs and treated with chemotherapy; selected eligibility criteria will be re-checked at this visit prior to randomization/treatment assignment and treatment.
- Visit 3 (Day 2, 3, 4 and/or 5, depending on PK sampling times), during which patients will have a PK sample(s) drawn and will be assessed for AEs and concomitant medications.
- Visit 4 (Day 6, 7 or 8), final visit, during which a PK sample will be drawn, patient diary will be collected and patients will be assessed for AEs, concomitant medications, overall safety and laboratory safety data.
- Visit 5 (Day 14 [+3]), follow-up visit or telephone contact for AEs and concomitant medications.

5.2 Study Procedures by Time Point

5.2.1 Visit 1 (screening, Day -14 to -1 or Day -7 to -1 for patients aged < 2 years)

If the Investigator considers a patient to be potentially eligible for the study, the written informed consent/assent for participation in the study must be obtained before any study-related procedures. The patient will be screened within 14 days (or within 7 days for patients aged < 2 years) prior to the first study drug administration and the following procedures will be performed/data collected during this visit:

- Informed consent signed by parent(s)/legal guardian(s) of the pediatric patient in compliance with the local laws and regulations. In addition signed children's assent form according to local requirements. Informed consent/assent may also be collected before Visit 1.
- Eligibility criteria.
- Demographic data (gender, race, date of birth).
- Medical and surgical history (including current cancer history and naivety to chemotherapy).
- History of nausea and vomiting in previous chemotherapy (if applicable).
- Prior and concomitant medications.
- Laboratory tests, including: hematology, serum chemistry and urinalysis. Urine samples will be obtained only if the patient is capable of providing a urine sample.
- Urine pregnancy test (for female patients having reached menarche only).
- Full physical examination.

- Vital signs (pulse rate, systolic and diastolic blood pressure), height/length, weight.
- 12-lead ECG (single recording).
- AE recording.
- ECOG PS (assessed for patients aged ≥ 10 years).
- Instruction to patient and to parent(s)/legal guardians of the pediatric patient on how to fill in the patient diary.

Based on the outcome of the assessments, the Investigator will be able to decide if the patient is eligible for the study.

5.2.2 Visit 2 (Day 1)

The following procedures will be performed/data collected:

- The patient will undergo pre-dose assessments, including confirmation of inclusion and exclusion criteria (local laboratory results from an appropriately certified local laboratory could be used at the discretion of Investigator to evaluate patients' eligibility; in case of ERT central ECG report pending, the assessment of compliance with exclusion criterion #21 could be made based on automatic interpretation of QTcB and QTcF results by ECG machine at the discretion of Investigator).
- Urine pregnancy test (for female patients having reached menarche only; if screening visit is performed on Day -1, it is not necessary to repeat the test on Day 1.).
- Concomitant medications and AEs recording
- Weight
- Treatment assignment / Randomization through IWRS.

After randomization/treatment assignment, the study drug administration schedule is the following:

- Netupitant will be administered based on the body weight as a single oral dose 1 h (± 10 minutes) prior to start of emetogenic (HEC or MEC) chemotherapy on Day 1.
- Palonosetron will be administered orally immediately (within 5 minutes) after netupitant, i.e., 1 h (± 10 minutes) prior to start of emetogenic (HEC or MEC) chemotherapy on Day 1.
- Any LEC or minimally emetogenic agent given, as part of the aforementioned chemotherapy regimens using HEC or MEC, is allowed at any time during the study and does not have any impact on the time of study drugs administration.

The date and the precise time (hh:mm) of the study drug administration must be recorded in the source records as well as on the relevant eCRF page for each medication given. Information on completeness of study drug administration must be recorded as well. The relevant tear-off labels from the study drugs kit will be attached to the drug administration form.

- PK sampling: a single blood sample will be collected from each patient within the time window from 2 to 8 h after netupitant administration. Sampling will take into account the time of the 12-lead ECG and vital signs (see below).
- Vital signs (pulse rate, systolic and diastolic blood pressure) will be obtained 4-6 h after study drugs administration, before PK sampling or at least 30 minutes after PK sampling.
- A 12-lead ECG (single recording) will be obtained 4-6 h after study drugs administration, before PK sampling or at least 30 minutes after PK sampling.
- The diary covering 120 h after start of emetogenic chemotherapy will be supplied to all patients. Patient or patient's parents/legal care holders have to record emetic episodes and use of any rescue medication.

5.2.3 Visit 3 (Day 2, 3, 4 and/or 5 depending on the PK sampling times)

The following procedures will be performed/data collected:

- Concomitant medications
- AEs recording
- PK sampling: a single blood sample will be collected from each patient within the time window from 24-48 h after netupitant administration. For pediatric patients ≥ 5 years, an additional PK sample will be collected from each patient within the time window from 72-96 h after netupitant administration.
- Review of patient diary and instructions. During the visit, after the diary has been reviewed, the patient will be asked to correct errors, omissions, or ambiguities, if any.

5.2.4 Visit 4 (final visit, Day 6, 7 or 8 depending on PK sampling times)

The following procedures will be performed/data collected:

- Concomitant medications
- Laboratory evaluations (hematology, serum chemistry and urinalysis; pregnancy test [(for female patients having reached menarche only])
- Full physical examination
- Vital signs (pulse rate, systolic and diastolic blood pressure; to be measured before PK sampling or at least 30 minutes after PK sampling)
- 12-lead ECG (single recording), before PK sampling or at least 30 minutes after PK sampling.
- AEs recording
- Check and retrieval of the completed patient diary
- PK sampling: a single blood sample will be collected from each patient within the time window from 120 to 168 h after netupitant administration.

5.2.5 Visit 5 (follow up visit, Day 14 [+3])

On Day 14 (+3) the following follow up procedures will be performed/data collected during a visit or via telephone contact:

- Concomitant medications
- AEs recording.

5.3 Definition of Completion

A patient will be defined as "completed" if s/he completes the study until Visit 5 (inclusive).

5.4 Premature Discontinuation

Patients may discontinue the study or may be withdrawn at any time for any of the following reasons:

- An AE that, in the opinion of the Investigator, makes it unsafe for the patient to continue the study. In this case, the appropriate measures will be taken.
- Any clinically significant laboratory abnormalities that in the Investigator's opinion endanger the patient.
- The patient's safety is affected by violation of inclusion or exclusion criteria.
- The patient and/or the parent(s)/ legal guardian(s) requests withdrawal from the study.
- The Investigator, for any reasons, terminates the entire study, or terminates the study for this patient; or the attending physician requests that the patient be withdrawn for any other medical reasons.
- The patient is unwilling or unable to adhere to the study requirements after randomization/enrollment, e.g., non-compliance.
- Whenever the study blind is broken by the Investigator, the patient will be automatically withdrawn from the study.
- The patient is lost to follow-up.
- The patient dies.
- The Sponsor or the Regulatory Authorities or the Ethics Committees, for any reason, terminates the entire study, or terminates the study for that patient or study center.

In all cases where a patient is withdrawn from the study, CRO must be informed immediately, and the date and reason for withdrawal must be recorded on the eCRF and in the patient's medical records. If more than one reason for withdrawal is recorded, the primary reason must be given.

If the patient is withdrawn due to an AE, including concomitant disease, full details of the event and treatment must be recorded in the patient's source documents and the eCRF. For non-serious AEs, the patient must be followed up until the cause of the event is established with follow-up information recorded up to 14[+3] days post-dose. For SAEs, the patient must be followed up until the cause of the event is established and should be followed up until they are completely resolved or until a stable condition has been

reached as no further improvement or change is expected according to conventional medical practice and according to the Investigator's judgment or until the patient is lost to follow-up (see Section 7.1.3 Reporting of Adverse Events and Section 7.1.4.1 Reporting of Serious Adverse Events).

If the patient is lost to follow up, all attempts to contact the patient should be documented in the patient's medical records.

All patients included in the study will be administered study drug (netupitant and palonosetron) on Day 1 (Visit 2); patients receiving the study drug will be evaluated regardless of completion of all study visits. An effort will be made to gather as much information as possible. Every attempt should be made to perform a final evaluation (Visit 4 procedures - see Flow Chart) for any patient who is withdrawn from the study for any reason excluding withdrawal of consent/assent. In addition, the Investigator must try his/her best to contact the patient within 14 to 17 days after the study drug administration to assess safety issues by collecting information suggestive of AEs and concomitant medications. Withdrawn patients will not be replaced. If the study is discontinued prematurely, all study materials (study drug, etc.) must be returned to the Sponsor. A written statement fully documenting the reasons for termination will be provided to the Investigators, the IEC/IRB, and Regulatory Authority (as appropriate to local regulations).

6 METHODS OF ASSESSMENT

6.1 Pharmacokinetic Assessments

The PK profiles of netupitant, its active metabolites M1, M2, M3, and palonosetron will be evaluated in pediatric cancer patients according to a sparse sampling schedule and a population PK approach.

A single blood sample will be collected from each patient in each of the following time windows:

- Pediatric patients ≥ 5 years: from 2 to 8 h, from 24 to 48 h, from 72 to 96 h, and from 120 to 168 h after netupitant administration.
- Pediatric patients < 5 years: from 2 to 8 h, from 24 to 48 h, and from 120 to 168 h after netupitant administration.

The actual sampling times will be recorded in the individual source documents and in the eCRF, and will be used in PK calculation.

The nominal number of plasma samples collected from all patients from each of the two treatment groups will be 154. The expected total number of plasma samples collected from the two treatment groups will be 308.

The volume of each blood sample will be 2.0 mL. For patient with body weight < 5.4 kg, the volume of each blood sample will be limited to 1.0 mL [38].

Data modelling will be based on a previous population PK study in adults receiving oral NEPA administration (study NETU-10-02 [26]). A two- compartment open model with first order absorption and elimination with lag-time adequately described the netupitant and palonosetron plasma concentration-time profiles, whereas a one-compartment model best fit the metabolite M1 and M3 concentration data, and a three-compartment model described the metabolite M2 data.

If the same structural models apply to the pediatric population, the typical values (TV) of the following structural model parameters will be assessed for netupitant and palonosetron:

- Ka: absorption rate constant for netupitant or formation rate constant for netupitant metabolites
- tlag: lag time
- Vi/F: apparent volume of compartment i, i.e., central and peripheral compartment(s), for extravascular administration
- CL/F: apparent systemic clearance for extravascular administration
- Q/F: inter-compartmental clearance

F is the absolute oral bioavailability for the parent compounds netupitant and palonosetron.

Different structural models could also be explored for netupitant, its metabolites, and palonosetron according to the findings of the present PK/PD study in pediatric patients after oral administration of netupitant and palonosetron. The final model parameters will

reflect the model structure and include possible continuous or categorical covariates that significantly correlate with PK parameters and explain inter-subject variability.

Individual model-predicted PK parameter values will be estimated from the final population pharmacokinetic models, based on mean population parameter values (typical values, TVs) and on the individual random effect (ηi). From final model parameters, individual plasma concentration-time profiles will be simulated and secondary PK parameters such as C_{max}, t_{max}, AUC and $t_{1/2}$ estimated by non-compartmental methods.

6.1.1 PK Sampling and Sample Handling

Blood samples will be collected for the determination of netupitant, netupitant metabolites, and palonosetron concentrations.

A total of 3 or 4 (only for pediatric patients aged ≥ 5 years) blood samples (2.0 mL each; for patients with body weight < 5.4 kg, the volume of each blood sample will be 1.0 mL) per patient will be taken according to the foreseen schedule.

The total number of data points from all patients will be 308. The total blood volume collected per patient will be approximately 3.0 to 8.0 mL.

In case of blood samples withdrawn from a central access or via an indwelling catheter, the cannula will be rinsed after each sampling with sterile saline solution containing 20 IU/mL Na-heparin. At each sampling time, the first ca.1.0 mL of blood will be discarded to avoid contamination of the sample with the Na-heparin solution. Then 2.0 mL blood (for patients with body weight < 5.4 kg, the volume of each blood sample will be 1.0 mL) will be collected into tubes containing K2-EDTA as anticoagulant. After collection, blood samples will be centrifuged immediately or stored, before centrifugation, in a refrigerator at +4 ± 2°C or in a melting ice bath for a maximum of 30 min. Centrifugation will be done by a centrifuge to obtain plasma.

Each plasma sample will be immediately divided into 4 aliquots (2 aliquots for patients with body weight < 5.4 kg) in pre-labeled polypropylene tubes: 2 aliquots (1 aliquot for patients with body weight < 5.4 kg) ≥130 µL each (sample and back-up sample) for the analysis of netupitant and its metabolites (M1, M2, M3), 2 aliquots (1 aliquot for patients with body weight < 5.4 kg) of ≥ 250 µL each (sample and back-up sample, for patients with body weight < 5.4 kg no back-up samples are to be obtained) for the analysis of palonosetron. Plasma samples will be stored frozen at -20° C or -70°C until analysis.

Further instructions on collection, handling, labeling, storage and shipment of PK samples are reported in the Laboratory manual.

6.1.2 Analytical Procedures

Netupitant, netupitant metabolites M1, M2 and M3, and palonosetron concentrations will be determined in plasma samples at an accredited bioanalytical laboratory.

Validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods with appropriate lower limits of quantification (LLOQ) will be used.

The method for the determination of netupitant and its metabolites requires a sample volume of 50 µL and has a LLOQ of 2 ng/mL for each analyte. For palonosetron determination, the method requires a sample volume of 100 µL and the LLOQ is 50 pg/mL.

Details of determination of netupitant, netupitant metabolites and palonosetron in human plasma of this clinical study will be included in the bioanalytical study plan. Analyses will be performed according to the general principles of "OECD Good Laboratory Practices for testing of chemicals" C(81)30(Final). The bioanalytical report will be appended to the CSR.

6.2 Efficacy Assessments

Efficacy assessments will be collected through a paper diary, which will be used to record emetic episodes and use of rescue medication. An emetic episode is defined as one or more continuous vomits (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents). Regurgitation (defined as the sudden effortless return of small volumes of gastric contents into the pharynx and mouth – typically after breastfeeding or bottle feeding) is a physiological event and must not be considered as an emetic episode (for patients up to 12 months of age). Patients, parents/guardians or caregivers should complete the diaries. Instructions on how to compile the paper diary will be given at the Screening Visit (Visit 1). Paper diary will be distributed at Day 1 (Visit 2) and will be collected at Final Visit (Visit 4).

6.2.1 Primary Endpoint

PK/PD relationship between netupitant exposure (AUC, C_{max}) and antiemetic efficacy in the delayed phase after a single oral netupitant administration, concomitantly with oral palonosetron, in pediatric cancer patients receiving HEC or MEC treatments. Efficacy parameter to be used in the correlation is the proportion of patients with CR (i.e., no emetic episodes and no rescue medication) during the delayed phase (> 24-120 h after the start of chemotherapy on Day 1).

6.2.2 Secondary Endpoints

- Pharmacokinetic (PK) endpoints:
  - AUC, C_{max}, t_{max} and $t_{1/2}$ of netupitant, netupitant metabolites M1, M2, M3, and palonosetron.
- Pharmacodynamic (PD) endpoints:
  - proportion of patients with complete response (CR, i.e., no emetic episodes and no rescue medication) during the delayed (> 24-120 h), acute (0-24 h), and overall phases (0-120 h) after start of chemotherapy administration on Day 1.
  - proportion of patients with no emetic episodes during the delayed (> 24-120 h), acute (0-24 h), and overall phases (0-120 h) after start of chemotherapy administration on Day 1.

- proportion of patients with no rescue medication during the delayed (> 24-120 h), acute (0-24 h), and overall phases (0-120 h) after start of chemotherapy administration on Day 1.

6.3 Safety Assessments

Safety assessments will consist of full physical examination (PE) and clinical laboratory tests (serum chemistry, hematology, urinalysis): these assessments will be performed at screening and at final visit (Visit 4). Moreover, vital signs measurements (pulse rate, systolic and diastolic blood pressure) and 12-lead ECGs (single recordings) will be obtained at screening, on Day 1 at 4-6 h after study drug administration, and at final visit.

Adverse events (AEs) will be monitored throughout the study.

6.3.1 Physical Examination

A full physical examination will be performed at Visit 1 (screening) and Visit 4 (Day 6, 7 or 8). This evaluation will include an examination of general appearance, head, eyes, ears, nose, throat, skin, neck, lungs, cardiovascular, breast, lymph nodes, abdomen, musculoskeletal and neurological. Information about the physical examination will be recorded in the source documentation at the site and in the eCRF. Significant findings/illnesses, discovered after the first study drug administration and which meet the definition of an AE, will also be recorded in the eCRF.

6.3.2 Vital Signs

Vital signs assessments will include: pulse rate, systolic and diastolic blood pressure, height/length (only at Visit 1, screening), and body weight (at Visit 1 and Visit 2). Pulse rate, systolic and diastolic blood pressure will be measured after the patient has been in the sitting or lying position for at least 5 minutes at Visit 1 (screening), Visit 2 (4-6 h after study drugs administration; Day 1) and Visit 4 (Final visit, Day 6, 7 or 8).

Vital signs shall be measured before PK sampling or at least 30 minutes after PK sampling.

6.3.3 12-lead ECG

Twelve-lead ECGs (single recording) will be recorded for each patient at Visit 1 (screening), Visit 2 at 4-6 h after study drugs administration, and Visit 4 (Day 6, 7 or 8, final visit). A digitally recorded ECG will be transmitted from the study site to a central reading facility, where ECG interpretations will be timely performed by a cardiologist (in case cardiologist's report is pending, the assessment of compliance with exclusion criterion #21 could be made based on automatic interpretation of QTcB and QTcF results by ECG machine at the discretion of Investigator). ECG interpretation scheme will include the analysis of the morphology, rhythm, conduction, ST segment, PR, QRS, QT and QTc intervals, T waves, U waves and the presence or absence of any pathological changes. The investigator will receive more detailed information regarding the ECG recording and assessment procedures in a separate manual.

After review of the results received from the central reading facility, the investigator must sign and date each ECG report.

ECGs shall be obtained before PK sampling or at least 30 minutes after PK sampling.

6.3.4 Clinical Laboratory Tests

The following parameters will be assessed at Visit 1 (screening) and Visit 4 (final visit):

a) Hematology: hematocrit, hemoglobin, erythrocytes (RBC), platelets, leukocytes (WBC), neutrophils, lymphocytes, basophils, eosinophils, monocytes.
b) Blood Chemistry: urea, creatinine/eGFR, total bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, potassium, albumin, total protein, blood glucose and total creatine kinase (CK).
c) Urinalysis: protein, glucose, WBC, RBC, and bacteria.

Female patients having reached menarche will have to undergo a urine pregnancy test at screening and on Day 1, as well as a blood pregnancy test on Visit 4 (final visit) as part of the clinical laboratory assessments.

All blood and urine samples collected at Visit 1 and Visit 4 will be sent to a central laboratory for analysis. Local laboratory results obtained from an appropriately certified local laboratory within the screening period could be used to support eligibility criteria at the discretion of Investigator. Only the confirmation of eligibility will be recorded in the eCRF as local laboratory values will not be entered into the eCRF.

After review of the results received from the central laboratory, the investigator must sign and date each laboratory report. The laboratory will provide normal reference ranges for the laboratory results report and will flag all abnormal values. The investigator will consider the values outside the normal range and repeat the test, if needed. In case clinically significant laboratory abnormalities are assessed by the Investigator, the etiology of the abnormality should be identified and the diagnosis should be recorded as an AE. Otherwise, if the etiology cannot be identified, the laboratory abnormality as such should be recorded as AE.

Clinically significant laboratory abnormalities (including those values ≥ grade 3 severity) detected after screening, if not justified by an underlying disease already recorded in the medical history, are to be recorded as AEs.

7 ADVERSE EVENTS

7.1 Method of Assessment

7.1.1 Definition of Adverse Events

Adverse Event (AE)

As defined by the current ICH Guideline for Good Clinical Practice [27] an Adverse Event (AE) is:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Within the scope of this study, such untoward medical occurrences would be considered as "AEs" even if the subject was not administered the study drugs but the subject (and/or subject's parent/guardian, as applicable) had already signed the Informed Consent/Assent Form.

This definition includes intercurrent illnesses or injuries, exacerbation of pre-existing conditions, and adverse events occurring as a result of drug withdrawal, abuse, medication errors, misuse or overdose. Adverse events observed during all periods of a clinical trial are to be recorded, including adverse events occurring during a period without trial medication.

Planned surgical interventions or planned hospitalizations scheduled prior to the Informed Consent but performed during the study should not be considered (serious) AEs.

Signs and symptoms considered as lack of efficacy (nausea and vomiting) and occurring during the study up to 5 days after the study drugs administration, will not be recorded on the AEs section of the eCRF, except on the condition that, in the investigator's opinion, nausea and vomiting are caused by any reason different from lack of efficacy of study drug or meet the definition of serious AE.

Serious Adverse Event (SAE)

A serious adverse event is any event that suggests a significant hazard, contraindication, side effect, or precaution, whether or not it is considered to be associated with the study product. A SAE is an AE that meets any of the following criteria:

- Results in death. This includes any death that occurs during the conduct of a clinical study, including deaths that appear to be completely unrelated to the study drugs (e.g., car accident).
- Is life-threatening. This includes any AE during which the subject is, in the view of the investigator, at immediate risk of death from the event as it occurs. This

definition does not include events that may have caused death if they had occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Other medical events that based upon appropriate medical judgment are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE.

Unexpected Adverse Event

An Unexpected Adverse Event is any experience not previously reported (in nature, severity or incidence) in the current IB for oral NEPA FDC [16].

Expedited Adverse Event Reporting

Any serious and unexpected AE that the Investigator or the Sponsor considers to be at least possibly related to study drug is subject to expedited reporting to the appropriate Health Authorities. Events for which causality is unknown/unassessable or unreported by the Investigator are considered to be possibly related.

Non-serious Adverse Events

Non-serious adverse events should be included in tabulations in the end-of-study and do not need to be submitted separately.

Preexisting Condition

A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

7.1.2 Classification of Adverse Events

The Investigator will classify AEs based on their severity and relationship to IMP.

Every effort must be made by the Investigator to categorize each AE according to its severity (see Section 7.1.2.1 Severity) and its relationship (see Section 7.1.2.2 Relationship to Investigational Medicinal Product).

7.1.2.1 Severity

The severity of an AE will be rated by the Investigator according to the descriptions and grading scales of the Common Terminology Criteria for Adverse Events (CTCAE) (for details please refer to the integral document Terminology Criteria for Adverse Events (CTCAE, Version 4.0, published: May 28, 2009 [v4.03: June 14, 2010]); U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute) [28], as summarized below:

Severity of AE according to CTC Grading Scale and related Guideline

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*;

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**;

Grade 4 Life-threatening consequences; urgent intervention indicated;

Grade 5 Death related to AE.

(*) Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

(**) Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.1.2.2 Relationship to Investigational Medicinal Product

For this trial, an AE cause and effect relationship to the study drug will be classified by the Investigator as reported hereafter.

Scale	Definition
Definitely Related	The evidence is compelling that the study drug caused the adverse event. There is a clear temporal relationship of the event to the study drug; the event is consistent with a known pattern of drug (or drug class) effects; the event cannot be explained by concurrent disease or other drugs or chemicals; the event diminished upon cessation of study drug exposure or reduction in dose; the event worsened or recurred upon unintentional re-exposure to the study drug (intentional rechallenge for the purpose of assigning causality should not be performed).
Probably Related	It is more likely that the event is due to the study drug than due to other etiologies, an alternative explanation is unlikely. There is a reasonable temporal relationship of the event to the study drug; the event may be consistent with a known pattern of drug (or drug class) effects; the drug seems more likely than other etiologies to cause the effect; the event diminished upon cessation of study drug exposure or reduction in dose.
Possibly Related	It is equally likely that the event is due to the study drug as it is due to other etiologies. There is a reasonable temporal relationship of the event to the study drug; follows a known or expected response pattern of the suspected drug but could also have been easily produced by a number of other etiologies.
Unlikely related	It is more likely that the event is due to other etiologies than due to the study drug. The event could have been reasonably related to patient's underlying diseases or concomitant treatments and/or the temporal relationship is doubtful between the study drug and the suspected adverse event. It the temporal relationship of the event to the study drug is reasonable, but there are important confounding factors/reasonably convincing alternative explanations, causality is considered unlikely.

Scale	Definition
Not related	The study drug almost certainly (or certainly) did not cause the event. Sufficient information exists to indicate that the etiology is unrelated to the study drug, e.g., the event is more likely related to patient's underlying diseases or concomitant treatments and/or there is no temporal relationship between the study drug and the suspected adverse event, e.g., the event occurred before the study drug was administrated.
Unassessable	The data are insufficient or contradictory to make a meaningful medical assessment.

7.1.3 Reporting of Adverse Events

AE reporting has to be in accordance with the ICH E6 Guidance on GCP and ICH E2A Guidance on Clinical Safety Management. [27, 29]

During the course of the study, all AEs (including SAEs), irrespective of the relatedness to the study drugs, will be recorded in detail in the source records and transcribed onto the AEs pages of the eCRF. During each monitoring visit, the site monitor will review all AEs and perform Source Data Verification (SDV). The investigator will be responsible for ensuring that the correct information concerning all AEs is entered on the appropriate eCRF pages.

The reporting period for AEs is the period starting from the time of Informed Consent Form signature and lasting until Visit 5 or up to 14[+3] days post-dose. All non-resolved AEs (including SAEs) beyond this date will be documented on the eCRF as “ongoing”.

7.1.4 Reporting of Serious Adverse Events

All SAEs occurring from the time of signing of the Informed Consent Form/Assent until 14[+3] days post-dose must be reported immediately to the CRO Pharmacovigilance e-mail address or sent by fax (see Section General Information).

The investigator or designated study coordinator must transmit the completed SAE Form to the CRO within 24 h of observation or notification of a SAE. All of these events must also be recorded on the appropriate eCRF pages.

It is the responsibility of the Investigator to inform his or her local Institutional Review Board (IRB)/Ethics Committee (EC) about SAEs according to the local IRB/EC requirements. It is the responsibility of the Sponsor (or Sponsor’s designee) to submit applicable SAE Reports to the Competent Authorities. Reporting of suspected unexpected serious adverse reactions (SUSARs) to the relevant IRB/EC, in accordance with the EU Clinical Trial Directive 2001/20/EC, the US Code of Federal Regulations 313.32 and ICH E6 Guidance on GCP and ICH E2A Guidance on Clinical Safety Management and all the applicable country regulations, will also be the responsibility of the Sponsor (or Sponsor’s designee). [27, 29]

A safety contact sheet will be provided to the investigator and will be maintained in the investigator file at the site. Refer to the instructions and definitions for completing the SAE Form and for submitting all SAEs to the CRO.

7.1.4.1 Follow-up of Serious Adverse Events

For safety monitoring purpose, SAEs will be followed up by the Investigator until they are completely resolved or until a stable condition has been reached as no further improvement or change is expected according to conventional medical practice and according to the Investigator's judgment or until the patient is lost to follow-up. When the investigational site receives any information about a serious adverse event which changes or adds information to the initial investigational SAE form, the site will fill out a new investigational SAE form, tick the"follow-up" box and send the form via e-mail or fax within 24 h to the CRO, especially if this new information has an effect on the seriousness, relatedness or expectedness of an adverse event.

7.1.4.2 Adverse Events of Special Interest

Special attention will be paid to QT prolongation and constipation, in particular to severe forms of constipation (CTCAE grade 3 or 4 [28]). In such cases, an accurate follow up will be performed by the Sponsor.

7.1.5 Pregnancy Report

In the unlikely eventuality that a patient becomes pregnant during the trial, the Investigator will be requested to complete the Pregnancy Report Form and any relevant document. They must be forwarded to the CRO pharmacovigilance e-mail address or sent by fax (see Section General Information) within 24 h of becoming aware of the pregnancy. Even though pregnancy is not considered as SAE itself, pregnancy has to be reported within the timelines defined for SAE.

Pregnant patients, as well as partners of male patients who become pregnant during the study, will be followed by the Investigator and CRO / Sponsor until the fetus / newborn is delivered. Reports of Pregnancy Outcome will be sent by the sites directly to Helsinn Corporate Drug Safety. The patient's/partner's primary care physician (or obstetrician) will be requested by the Investigator to provide further information on the pregnancy outcome and to complete the Pregnancy Information Letter. If pregnancy occurs in a female patient between the screening and randomization phase, that patient will be removed from the study.

8 STATISTICS

This section summarizes the statistical principles and methods planned to analyze the data for this clinical study. The reference document is the ICH Topic E9 Statistical Principles for Clinical Trials: Note for Guidance on Statistical Principles in Clinical Trials [30].

Further details of the statistical analyses and data presentations to be used in reporting the study will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to data analysis.

8.1 Sample Size Determination

A total of 92 pediatric patients (i.e., 46 for each treatment group) will be enrolled in the study.

For each age class used for stratification, a sample size was computed. Each age class is powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of clearance with at least 80% power.

The sample size was computed for the following age classes: Birth-<1 month, 1 <3 months, 3-<6 months, 6-<12 months, 1-<2 years, 2-<5 years, 5-<12 years, 12-<18 years.

Variability of clearance in each pediatric age class was estimated based on the same model used to determine the dose to be administered, which is:

$$\mathrm{Log(CL/F)p} = \log(\mathrm{CL/F)a} + \mathrm{ADE} * \log(\mathrm{BWp}/70)$$

where (CL/F)p and (CL/F)a are the systemic clearances in pediatric patients and adults, respectively, BWp is the body weight of children and ADE is an age-dependent exponent considered constant within each age class.

Variance of log (CL/F)p was then calculated as:

ADE^2 * Variance (log (BWp))

considering log (CL/F)a as a constant term.

Variance (log (BWp)) was obtained from published data in Fryar et al 2012 [31], where mean values in each age class and related standard errors were available.

Based on these data, the variance of log weight was obtained as:

Variance (BWp) = standard $error^2$ * N

and

Variance (log BWp) ≈ Variance (BWp) / $Mean^2$

(i.e., no assumption on the statistical distribution was made);

The table below reports the values as selected from published data in Fryar et al 2012 [31] and the further elaboration

Age class planned for the study	Age class [31]&	Weight (kg) N/ Mean / SE / gender [31]	ADE	Estimated SD (BWp)	Estimated SD (log BWp)	Estimated SD (log CL/F)
Birth to <1 month	Birth-2 months	82 / 5.0 / 0.11 / F	1.2	1.00	0.199	0.239
1 to <3 months	Birth-2 months	82 / 5.0 / 0.11 / F	1.2	1.00	0.199	0.239
3 to <6 months	3-5 months	111 / 7.1 / 0.11 / M	1	1.16	0.163	0.163
6 to <12 months	6-8 months 9-11 months	103 / 8.7 / 0.13 / M 108 / 9.6 / 0.15 / M *	1 1	1.32 1.56	ND 0.162	ND 0.162
1 to <2 years	1 year	297 / 10.9 / 0.10 / F	1	1.72	0.158	0.158
2 to <5 years	3 years	191 / 15.7 / 0.24 / F	0.9	3.32	0.211	0.190
5 to <12 years	9 years	191 / 36.6 / 1.17 / M	0.75	16.2	0.442	0.331
12 <18 years	17 years	188 / 77.4 / 2.41 / M	0.75	33.0	0.427	0.320

& only data related to the age period actually used for the sample size calculations are reported in this table.
* given that mean values were very similar, data from the class with the larger SD of weights was used
ADE = age-dependent exponent; BWp= body weight of children; CL/F= systemic clearance; F= Female; M = Male; ND= Not Done; SD = Standard Deviation

Sample size was then computed by the R program described in Wang et al 2012 [32] for each age class.

The resulted sample size for each treatment group, and the relevant power are provided in the table below:

Age class for the study	N estimated / dose	Power
Birth to < 1 month	6	0.891
1 to <3 months	6	0.891
3 to <6 months	4	0.832
6 to <12 months.	4	0.836
1 to <2 years	4	0.854
2 to <5 years	5	0.913
5 to <12 years	8	0.830
12 to <18 years	8	0.865

In order to facilitate the management of the study, the calculated sample size in the age class 2 to <5 years will be rounded up to 6 patients.

8.2 Definition of Study Populations for Analysis

The following analysis populations are defined:

The **Full Analysis Set** (FAS) includes all patients randomized or to whom a study drug was assigned and who received a HEC or MEC regimen and the entire planned volume of netupitant and palonosetron. Following the intent-to-treat principle, patients will be assigned to the treatment group according to the treatment assigned/randomized. FAS will be used for demography, other baseline characteristics and efficacy analyses.

The **PK population** includes all patients who received the entire planned volume of netupitant and/or the entire planned volume of palonosetron and who have at least one measurable concentration of netupitant and/or palonosetron. PK population will be used for all PK analyses.

The **Safety** population includes all patients who received at least part of the planned volume of netupitant or at least part of the planned volume of palonosetron. Patients will be assigned to treatment groups according to the actual treatment received. Safety population will be used for demography, other baseline characteristics and for all safety analyses.

8.3 Statistical Analysis

General Considerations

General descriptive statistics for numeric variables will include n (number of observed values), mean, standard deviation (SD), median, minimum and maximum values. For categorical variables, the number and percentage of patients will be presented.

8.3.1 Missing Data

Due to the descriptive nature of the analysis, no procedure for handling missing data will be applied to pharmacokinetic or safety data.

For the efficacy analysis, any patients who do not provide data about occurrence of emetic episode and rescue medication intake after chemotherapy administration (which are needed to assess CR) will be considered as treatment failures in the relevant phase with missing information.

The same approach will be also applied to each component of CR, i.e. emetic episodes and rescue medication intake.

8.3.2 Covariates, Interactions and Subgroups

There are some factors expected to influence the efficacy endpoints, i.e., age class, emetogenicity of chemotherapy and schedule of chemotherapy. These factors will be taken into consideration for randomization. Efficacy endpoints will be presented by strata.

8.3.3 Analysis of Demographics and Baseline Variables

Demographics and baseline characteristic will be summarized by treatment group by means of descriptive statistics, in addition to be listed. Descriptive statistics will be presented overall and by strata.

8.3.4 Pharmacokinetic Analysis

Exploratory PK analyses will be applied to evaluate in the pediatric population the disposition characteristics of netupitant, its metabolites and palonosetron observed in adult patients. The initial population PK model (base model) will be developed by comparing structural models and random error models based on parameters such as the objective function values, the log-likelihood values, the Akaike's and the Bayesian's Information Criteria (AIC and BIC), the residual errors, the random distribution in conditional weighted residual plots, the graphical correlation between the observed versus predicted concentration values.

The final population PK model will include possible additional fixed effects represented by relevant covariates that will prove to correlate with one or more population PK parameters and contribute to significantly explain and minimize the inter-subject variability.

The final model will be qualified via a visual predictive check.

Inter-subject / inter-occasion variability (level 1 random-effect) and observation-level random error (level 2 random effect) will also be modeled.

Individual model-predicted PK parameter values will be estimated from the final population pharmacokinetic models, based on mean population parameter values (TVs) and on the individual random effect (ηi). Individual plasma-concentration-time curves will be simulated from final model parameters, and secondary parameters such as C_{max}, t_{max}, AUC and $t_{1/2}$ estimated by non-compartmental methods.

Mean and coefficient of variation (CV) of the pharmacokinetic parameters will be calculated from the individual predictions.

The effect of continuous and categorical covariates on the PK parameter variability will be evaluated by step-wise forward addition and backward elimination procedures. Continuous covariates will include at least age, BW, albumin, total bilirubin, creatinine, ALT, AST, ALP. Categorical covariates will include at least gender, chemotherapy schedule, HEC/MEC, rescue medication (yes/no), concomitant medications.

Adult data from previous population PK study NETU-10-02 [26] after oral administration of the netupitant-palonosetron fixed combination will be used as prior information and included in the analysis.

8.3.5 Efficacy Analyses

All results will be interpreted in a descriptive manner, since the study is not powered to compare the treatment groups for the efficacy assessments.

For each phase (delayed, acute, and overall), numbers and percentages (including 95% CI) of patients with CR, with no emetic episodes and no rescue medication will be summarized by treatment. The difference in response rate between the groups and relevant 95% CI will be provided as well.

Efficacy analysis will be presented for the overall population and by strata.

8.3.6 Pharmacokinetic/Pharmacodynamic Analysis

PK/PD relationships between predicted individual exposure metrics (C_{max} and AUC) of netupitant versus efficacy (CR delayed phase) will be investigated via graphical exploratory analyses. In addition, a logistic regression analysis will be used to link the exposure metrics (C_{max}, AUC) to categorical response (CR delayed phase).

The dose-exposure relationship and the PK/PD correlation (exposure-response relationship) for netupitant in pediatric cancer patients will be compared to that observed in adult cancer patients in order to support the dose selection for netupitant in the pediatric population. Similar exposures in adult and pediatric patients are assumed to produce similar efficacy.

8.3.7 Safety Analyses

All AEs will be listed by SOC, described and summarized by frequency tables. Summaries will be made by treatment arm with respect to the percentage of patients having at least one occurrence of that event during the study and the total number of events.

For safety analysis, the laboratory data will be analyzed and described as follows: listings (including flag for values outside the normal range), count (number and percentage) of value below, within and above normal range, descriptive statistics for change from baseline values. Shift tables with respect to normal range (Low/Normal/High) will be presented. ECG data will be summarized highlighting differences from baseline for quantitative variables and frequencies of treatment emergent abnormalities. Vital signs will be summarized using descriptive statistics for observed values and change from baseline, in addition to being listed.

Safety analysis will be presented for the overall safety population and by strata.

8.4 Interim Analysis

No interim analysis is planned for this study.

9 DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will be convened for the evaluation of safety data during the study. The DSMB will not include employees of the Sponsor. Composition, role and responsibilities of the DSMB will be given in a separate document named DSMB charter. The purpose of the DSMB is to perform a qualitative safety assessment. Study data will be provided to the DSMB, as foreseen by the study design and at periodical intervals. Any additional information will be promptly made available by the Sponsor upon request of DSMB members.

The DSMB will have periodical face-to-face and/or telephone meetings, as appropriate and as foreseen by the study design, and a set of minutes will be issued after each meeting. A charter for the DSMB will be completed before patients enrollment begins.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Ethical Considerations

The study will be performed in accordance with the principles contained in the Declaration of Helsinki [33] as amended by the World Medical Association in Fortaleza in 2013, and the ICH GCP guidelines as well as all local laws and regulations of the USA and other countries where the study is conducted, as applicable.

10.1.1 Laws and Regulations

This clinical study will be conducted in compliance with all international laws and regulations and national laws and regulations of the USA and other countries wherethe trial is performed, as applicable, as well as any applicable guidelines.

10.1.2 Patient's Information Sheet, Informed Consent Form and Assent Form

Before starting any study-specific evaluations or procedures, parent(s)/legal guardian(s) of all patients invited to participate in the study and patients of appropriate age and intellectual maturity as defined by local laws and regulations must be given written and verbal information about the aims, methods, anticipated benefits and potential hazards of the study. Furthermore, the patients and their parent(s)/legal guardian(s) must be notified that participation is voluntary, and that the patient is free to withdraw from the study at any time without any disadvantages for the patient's subsequent care. The parent(s)/legal guardian(s) is/are also free to withdraw their child from the study at any time without any disadvantages for the child's subsequent care.

In addition, parent(s)/legal guardian(s) will be given the Information for Parents and Informed Consent Form in native language expressed in clear, concise and lay language for review and consideration. As required by local laws and regulations, all patients of appropriate age and intellectual maturity will be given the Children's Information Sheet and Assent Form explaining the study in age-appropriate terms.

Information for Parents and Informed Consent Form as well as the Children's Information Sheet and Assent Form will tell potential patients and their parent(s)/legal guardian(s) about the nature of the drugs, its efficacy and safety profile, the route of administration, and the available clinical experiences in humans. It will also outline the steps of the protocol as they will apply to the individual including the number of visits, the number of procedures and types of assessments/measurements to be performed so that the individual has a clear picture of the risks, inconveniences and benefits that may accrue.

The patients and their parent(s)/legal guardian(s) must also know that patient's personal medical records may be reviewed in strict confidence by the Sponsor's staff or representatives and by Regulatory Authorities and Independent Ethics Committees(IEC)/Institutional Review Board (IRB) and that personal information about

patients will be held on a confidential database. Conditions for ensuring the anonymity of data and the security and confidentiality of the database should be explained.

Both the Informed Consent Form and the assent form must be previously approved by relevant IEC(s)/IRB and may further be updated as new important information becomes available that may affect patient's or parent(s)/legal guardian(s) willingness to participate or continue in the trial.

Written Informed Consent Form signed by the parent(s)/legal guardian(s) must be obtained prior to enrollment of all pediatric patients and the signed assent form should be obtained from all patients of appropriate age and intellectual maturity in compliance with local laws and regulations.

Two copies of the Informed Consent Form and Assent Form shall be signed. The Investigator shall provide one signed copy of the Informed Consent Form to the parent(s)/legal guardian(s) and one copy of the assent form to the child (if applicable), and will keep the second copy of the original signed forms in the Investigator's study file.

10.1.3 Protocol Amendments

Changes to the protocol may only be made by means of a written amendment, which has to be approved and signed by the authorized individuals of the Sponsor and by the Investigator. The study code, the title of the study, the progressive number and the date of the amendment must be recorded on the first page of the document. Exhaustive justifications that motivate the amendment to the protocol should clearly be addressed in the document. All protocol amendments must be submitted to the EC/IRB for review and approval (as well as to Competent Authorities, where applicable for authorization) unless it covers administrative issues only. In this case, the EC/IRB and Competent Authorities will be notified of the amendment for information purposes only, as applicable.

10.1.4 Protocol Deviations

The Investigator has to conduct the study in accordance with the approved current protocol and will not be allowed to make any changes with the only exception when immediate changes are necessary to protect the safety, rights, and welfare of the patient.

In order to obtain interpretable results, neither the Investigator nor the Sponsor/CROs will alter the study conditions agreed upon and set out in this protocol.

In the event that an isolated, unforeseen instance resulting in a protocol deviation occurs, the Investigator is to document this deviation and notify it to the clinical CRO as soon as possible, in writing. In no instance should this increase the patient's risk or affect the validity of the study data.

10.1.5 Data Collection

Electronic Case Report Forms (eCRFs) will be used for recording patient's study data using a validated web-based Electronic Data Capture (EDC) system. It is the responsibility of the Investigator to ensure that the eCRFs are properly and completely filled in. The eCRFs must be completed for all patients who have been included in the

study. A screening log will be completed for screening failures. Data of these patients will be handled separately from the data of patients included in the study.

Each authorized site personnel will be assigned a login and password to enter the EDC system via a secure network. Each login uniquely identifies the user and appropriate permissions will be set-up according to the user role. The access to the system will be granted once the user's training will be completed and documented.

Data Clarification Forms (DCFs) will be used to validate/clarify data entered on an eCRF page. Some DCFs will be generated automatically by the system when the user saves data that does not meet the criteria pre-defined for the data field. In addition, other DCFs will be created manually.

Discrepancies raised will be reviewed online to determine the corrective action needed. Changes will be made directly by authorized site staff. The EDC system's audit trail will keep track of any information entered, modified and deleted. The audit trail will include, as a minimum, what was entered/changed/modified, who made the action and when the action was made. Any answered DCF will be reviewed and closed by authorized users. The Investigator will electronically sign the eCRF to validate the content.

Patient's source documentation (i.e., hospital charts) will be maintained at the clinic/hospital. Source data to be recorded directly onto the eCRFs will be communicated in advance. In cases where source documents are not eCRFs, the information on the eCRFs must match the source documents. Source data verification will be regularly performed by the blinded study monitor.

10.1.6 Monitoring and Quality Assurance

The study will be monitored by CRO's adequately qualified and trained clinical monitors on a regular basis throughout the study period to ensure the proper conduct of the clinical trial. The purposes of clinical trial monitoring are to verify that the rights and well-being of study patients are protected, that the reported trial data are accurate, complete and verifiable against the source documents, and that the study is conducted in accordance with the current protocol, GCP guideline and applicable regulatory requirements. During the monitoring visits, monitors will verify the following including but not limited to: patient/parental Informed Consent Form/Assent Form, patient's eligibility, safety data and reporting, quality of source documents and eCRF data against patient's medical records. If inconsistencies are identified, the corresponding corrections to the eCRF data will have to be made by the Investigator. Monitors will also check patient compliance, accrual, drug handling, including dispensing procedures and accountability logs, delegation of responsibilities within the Investigator's team, relevant communications with family doctors, if any, ancillary equipment and facilities, including refrigerators and freezers, local labs, etc. The Investigator and other site staff involved in the study must allocate enough time to the monitor at these visits.

Upon request by the Sponsor, or following the CRO's audit plan, on-site study audits will be conducted in order to ensure the study is in compliance with GCP, applicable regulatory requirements, and the study protocol. The auditing activities may also be conducted after study completion.

In addition, Regulatory Authorities may wish to conduct on-site inspections (during the study or after its completion). If a Regulatory Authority notifies the Investigator of an inspection or visits the site unannounced for purposes of conducting an inspection, the Investigator must inform the study Sponsor and CRO immediately. The Investigator will make all efforts to facilitate the conduct of the audits and inspections giving access to all necessary facilities, data and documents.

10.1.7 Study Documentation and Records Retention

The medical (hospital) files of trial patients should be retained in accordance with national legislation (and in accordance with the maximum period of time permitted by the hospital (or institution/private practice).

The Sponsor should ensure that it is specified in the protocol or other written agreement that the Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/EC review, and regulatory inspection(s), providing direct access to source data/documents.

All the essential study documents [27] should be retained at the sites until when the Sponsor informs the Investigators/institutions in writing the date when the trial related records are no longer needed and in any case in accordance with FDA regulation 21 CFR 312.62(b) and (c) and ICH-GCP guidelines. Should the Investigator wish to assign the study documentation to another party or move to another location, the Sponsor should promptly be notified.

10.1.8 Confidentiality

The Sponsor and the CRO must ensure that the Investigator keeps secret from third parties any confidential information disclosed or provided by the Sponsor and regarding the Sponsor and its study-related products. The Investigator agrees to use such information only to accomplish the present study tasks and not to use it for any other purposes without the prior written consent by the Sponsor. Prior to the study start-up, each Investigator as well as each subcontractor to be involved in the study should sign a confidentiality agreement with the CRO acting for and on behalf of the Sponsor.

10.1.9 Publication Policy

As a general rule, the Sponsor and the Investigator(s) agree that no publications presenting or discussing data and/or results from clinical trials sponsored by Helsinn Healthcare SA will take place until the participating center(s) has/have completed the study, the data have been interpreted, and the final report has been issued. As a rule, the Sponsor is free to use the data collected in the sponsored study for the drug registration, world-wide scientific product documentation, and for publication. In general, the Sponsor has no objections if the Investigator publishes the results of the study obtained by the Investigator/Institution sponsored by Helsinn Healthcare SA; however, the Investigator is requested to provide the Sponsor with a copy of the manuscript for review before submitting it to the publisher with a cover letter informing the Sponsor about the intention to publish the study results. Such a procedure is necessary to prevent premature disclosure of trade secrets or otherwise patent-protected material and is not intended as a

restrictive measure concerning the study results or the opinions of the Investigators. After the review of the manuscript by the Sponsor, the Investigator will be provided with the Sponsor's comments, if any, and the opinion of the Sponsor regarding study results publication. The Investigator shall however consider the Sponsor's comments and proposed revisions. If requested by the Sponsor, the Investigator shall delay the presentation or publication of the study data in order to allow the Sponsor sufficient time to obtain Intellectual Property Protection. The Sponsor is entitled to include as authors of the publication all Sponsor's personnel who have contributed substantially to the theoretical or experimental activities and also to make a decision on the order in which the authors' names will be given. Costs for publication must be regulated by written agreement between the parties. For multicenter studies, the Investigators who will be quoted as authors of the publication(s) should be agreed upon with the Sponsor. If publication of the results of the study, either in part or in full, is prepared by the Sponsor, the Investigator(s) will be asked in writing if he/she/they agree(s) to be listed as one of the authors of the publication. Answers should be sent in writing to the Sponsor within a reasonable time limit (30 days).

10.1.10 Insurance

The Sponsor will obtain liability coverage compliant with the regulations of each country involved in the study. This insurance will cover health impairments resulting from drugs and/or substances/investigational products administered in the course of this study for which the patient (and/or patient's parent or guardian) has given his/her written Informed Consent/Assent. This insurance also covers health impairments resulting from study procedures.

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12 APPENDICES

Appendix 1: Treatment scheme

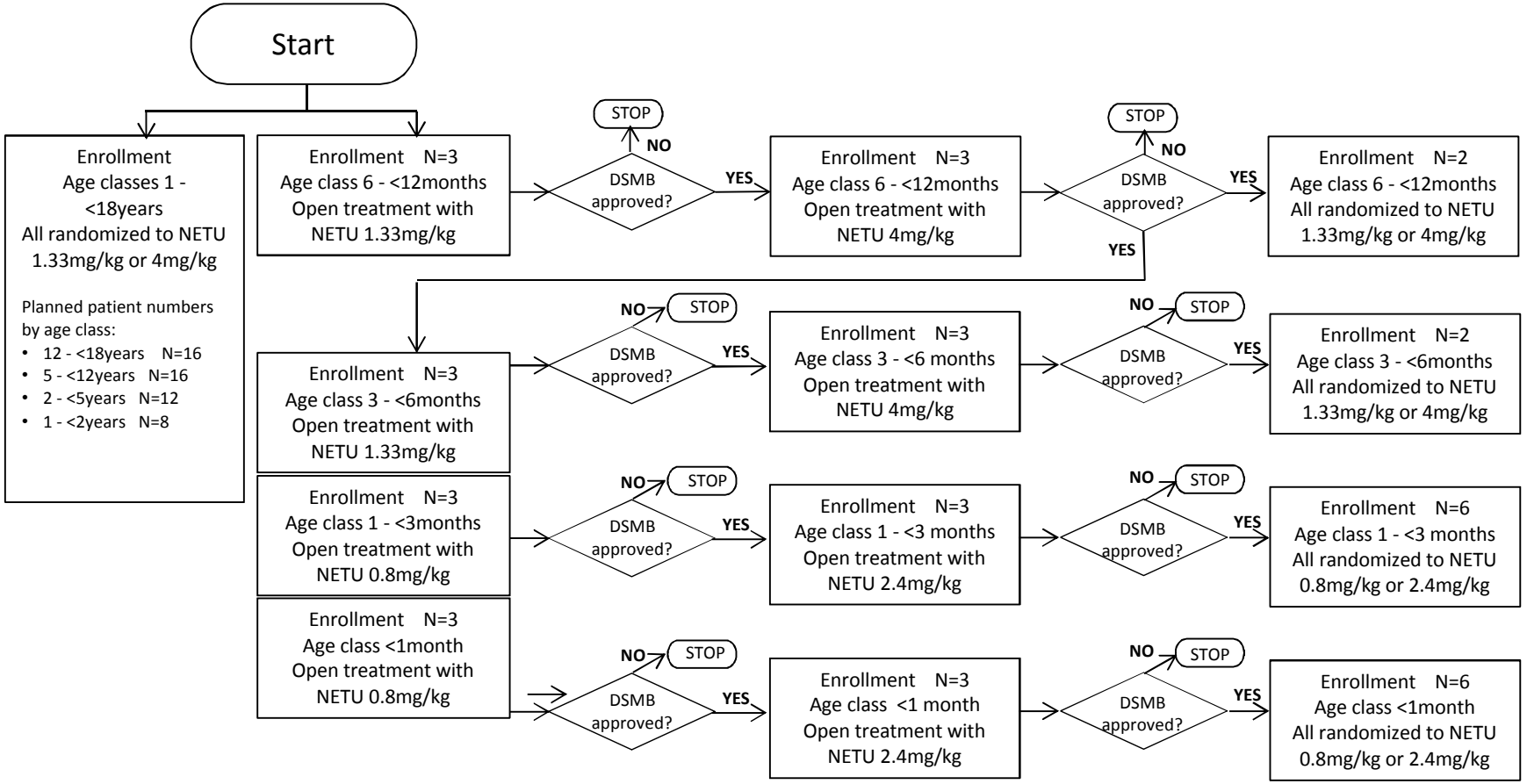
Appendix 2: Emetogenic potential of IV and oral antineoplastic agents

Appendix 3: Eastern Cooperative Oncology Group Performance Status (ECOG PS)

Appendix 4: List of CYP3A4 Inducers, strong and moderate Inhibitors, and Substrates

Appendix 5: Schwartz equation for determining estimated glomerular filtration rate (eGFR)

Appendix 1: Treatment Scheme



Appendix 2: POGO Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients [35]*

Emetogenicity	IV Agents	Oral Agents
High (>90% frequency of emesis in absence of prophylaxis)	Altretamine Carboplatin Carmustine >250 mg/m^2 Cisplatin Cyclophosphamide ≥1 g/m^2 Cytarabine 3 g/m^2/dose Dacarbazine Dactinomycin Mechlorethamine Methotrexate ≥12 g/m^2 Streptozocin Thiotepa ≥300 mg/m^2	Procarbazine
Moderate (30–90% frequency of emesis in absence of prophylaxis)	Aldesleukin >12 to 15 million U/m^2 Amifostine >300 mg/m^2 Arsenic trioxide Azacitidine Bendamustine Busulfan Carmustine ≤ 250 mg/m^2 Clofarabine Cyclophosphamide <1 g/m^2 Cytarabine >200 mg/m^2 to <3 g/m^2 Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Intrathecal therapy (methotrexate, hydrocortisone, and cytarabine) Irinotecan Lomustine Melphalan >50 mg/m^2 Methotrexate ≥ 250 mg/m^2 to <12 g/m^2 Oxaliplatin >75 mg/m^2	Cyclophosphamide Etoposide Imatinib Temozolomide Vinorelbine

Emetogenicity	IV Agents	Oral Agents
Low (10 to <30% frequency of emesis in absence of prophylaxis)	Amifostine ≤300 mg/m^2 Amsacrine Bexarotene Capecitabine Cytarabine ≤ 200 mg/m^2 Docetaxel Doxorubicin (liposomal) Etoposide 5-Fluorouracil Gemcitabine Ixabepilone Methotrexate >50 mg/m^2 to <250 mg/m^2 Mitomycin Mitoxantrone Nilotinib Paclitaxel Paclitaxel-albumin Pemetrexed Teniposide Thiotepa <300 mg/m^2 Topotecan Vorinostat	Busulfan Fludarabine
Minimal (<10% frequency of emesis in absence of prophylaxis)	Alemtuzumab Alpha interferon Asparaginase (IM or IV) Bevacizumab Bleomycin Bortezomib Cetuximab Cladribine (2-chlorodeoxyadenosine) Dasatinib Decitabine Denileukin diftitox Dexrazoxane Erlotinib Fludarabine Gefitinib Gemtuzumab ozogamicin Lapatinib	Chlorambucil Hydroxyurea Melphalan (low-dose) Mercaptopurine Thioguanine

Emetogenicity	IV Agents	Oral Agents
	Lenalidomide Methotrexate ≤ 50 mg/m^2 Nelarabine Panitumumab Pentostatin Rituximab Sorafenib Sunitinib Temsirolimus Thalidomide Trastuzumab Valrubicin Vinblastine Vincristine Vindesine Vinorelbine	

* Although not mentioned in this POGO Guideline, Temozolomide given intravenously should be considered as moderately emetogenic chemotherapy (MEC).

Appendix 3: Eastern Cooperative Oncology Group Performance Status (ECOG PS)

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Oncol:
Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group; Am J Clin Oncol 5:649-655; 1982 [34].

Appendix 4: CYP3A4 and CYP2D6 Inhibitors, Inducers and Substrates

Strong inhibitors: ≥ 5-fold increase in AUC or > 80% decrease in CL

Moderate inhibitors: ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL

Strong inducers: ≥ 80% decrease in AUC

Moderate Inducers: 50-80% decrease in AUC

Type	Agent
Strong and Moderate Inducers	Strong CYP3A4 inducers: carbamazepine, phenytoin, rifampin, St. John's wort Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin Strong and moderate CYP2D6 inducers: none known
Strong and Moderate Inhibitors	Strong CYP3A4 inhibitors: boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole Moderate CYP3A4 inhibitors: amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil Strong CYP2D6 inhibitors: bupropion, fluoxetine, paroxetine, quinidine Moderate CYP2D6 inhibitors: cinacalcet, duloxetine, terbinafine
Substrates with narrow therapeutic range	CYP3A4: alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine CYP2D6: thioridazine

Lists of in vivo inhibitors, inducers and substrates are taken from the following FDA website:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Appendix 5: Schwartz equation for determining estimated glomerular filtration rate (eGFR)

eGFR = 0.413 x height (cm)/serum creatinine (mg/dl)

To convert serum creatinine from µmol/l to mg/dl, the following equation should be used:

Serum creatinine (mg/dl) = Serum creatinine (µmol/l) x 0.0113

Schwartz GJ and Work DF, 2009 [36]