16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

NEPA-17-05 Amended protocol (v3.1) 30 NOV 2017

Amendment #3, 30 NOV 2017

Only Protocol v3.1 dated 30Nov2017 was used for study patient enrollment purposes. All previous versions and related amendments are available in the eTMF.

Study Title

A multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group phase 3b study to assess the safety and to describe the efficacy of IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) compared to oral netupitant/palonosetron (300 mg/0.5 mg) combination (Akynzeo®) for the prevention of chemotherapy-induced nausea and vomiting in initial and repeated cycles of anthracycline-cyclophosphamide (AC) chemotherapy in women with breast cancer

Study Number	NEPA-17-05
Protocol Version	Final (v3.1)
Protocol Date	30 NOV 2017
Sponsor	Helsinn Healthcare SA Via Pian Scairolo 9 6912 Lugano, Switzerland Phone: +41 91 985 21 21 Fax: +41 91 985 21 22
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The clinical trial will be conducted, and essential study documentation archived, in compliance with this protocol, applicable SOPs and standards, which incorporate the requirements of the ICH Guideline for Good Clinical Practice.

Document History

With respect to v1.0, in v1.1 minor typing errors have been corrected in the numbering sequence of Inclusion criteria in the Synopsis and in Section 4.3.2 Inclusion criteria.

With respect to v1.1, in v1.2 the study procedure has been modified allowing screening activities to be performed / completed on Day 1 (and consequently the date of Visit 1 and Visit 2 may coincide). Screening period is now therefore defined as the period from Day -14 to Day 1. The text has been modified throughout the protocol where applicable accordingly.

The number of planned study sites was updated from "approximately 45 sites in the US" to "approximately 50 to 75 sites in the US".

In addition, some wording has been slightly improved throughout the protocol, as well as some minor errors have been corrected.

With respect to v1.2, in v2.0 the number of planned study countries and sites was updated from "approximately 50 to 75 sites in the US" to in addition "approximately 33 sites distributed in Russia, Ukraine, Belarus and Georgia".

An additional CRO, i.e., PSI CRO AG, has been added for activities related to EU region.

A dedicated Section 4.1.1 Definition of patients naivety/non-naivety has been added to further improve definition of naivety/non-naivety to any chemotherapy.

The factor "region" has been added to the list of stratification factors having an impact on Primary efficacy analysis.

In addition, some wording related to these changes has been slightly improved throughout the protocol, i.e., in Section 5.5 Packaging and Shipment, 5.7 Drug Depots, 5.9 Administration of Study Treatment, 5.11. Randomization-Use of IWRS, 5.14 Prior and Concomitant Medications.

With respect to v2.0, in v3.0 the study design has been modified from a non-inferiority efficacy study to a safety study. The primary objective is now to assess safety of IV fosnetupitant/palonosetron combination (IV NEPA FDC), and the secondary objective is to describe the efficacy. As a result, there will be no formal inference testing included in the analysis and data will be subject to descriptive analysis only.

The number of chemotherapy cycles was increased from one cycle to the first 4 chemotherapy cycles (as maximum). Visit 4 will be the end of each "Study Cycle", and Visit 5 (HEOR Extension) has been deleted.

Sample size was also lowered to 400 patients equally randomized to each arm. Study drug assignment for Cycles 2 to 4 will be closed 7 days after the last (400^{th}) patient is randomized, in order to permit patients already screened for a subsequent study cycle to be administered study drug. Patients still participating in the study at this time should complete their current cycle and will not be allowed to enter in a subsequent study cycle.

Inclusion #4 has been changed to enrol patients naïve to moderately or highly emetogenic antineoplastic agents, rather than only naïve to AC chemotherapy. This change also eliminates the stratification by naivety to any emetogenic antineoplastic agent. Inclusion #5 has also been updated to specify that patients must be scheduled to receive at least 4 consecutive cycles of an AC regimen, in line with the change in study design to include repeated cycles. Additional clarifications were also added regarding inclusion/exclusion criteria to be checked prior to each repeated cycle.

In terms of safety, laboratory assessments have been added at Visit 1 and Visit 3 of each cycle, where select parameters will be measured and assessments (below, within and above normal range) will be summarized. The urine pregnancy test at Visit 3 was deleted. The definitions of treatment-emergent adverse events, the reporting periods for adverse events, and the planned summaries for adverse events, have all been updated to account for repeated cycles.

For efficacy assessments, the patient diary will be administered during each cycle, while the FLIE questionnaire will only be administered during Cycle 1 and Cycle 2. Complete protection (CP) has been removed as an efficacy endpoint. All efficacy analyses will now be descriptive only.

For the exploratory HEOR evaluations, information on emergency department and in-patient admissions, as well as chemotherapy, will be collected during each cycle, while WPAI questionnaire will only be administered during Cycle 1 and Cycle 2. CINV prophylaxis will no longer be collected as all patients will remain on either IV fosnetupitant/palonosetron or oral netupitant/palonosetron during each cycle in this study.

Belarus has been removed as potential country for this study, and approximate numbers of study sites have been adjusted accordingly. Updates to Study Drug Mananagment procedures have also been made. In addition, the General Information section has been updated with appropriate CRO contacts.

Wording related to these changes has been implemented throughout the protocol.

With respect to v3.0, in v3.1 minor typing errors have been corrected in the numbering sequence of Exclusion criteria in Section 4.3.3 Exclusion criteria, steps in Section 5.4 Dose and Administration, and reasons for discontinuations in Section 6.4 Premature Discontinuation. Study title on coverpage was also corrected as “nausea” was inadvertently omitted, and the main phone number for George Clinical was updated on the coverpage and in the General Information section. Detail about study drug administration was added to Section 5.9 Administration of Study Treatment.

Signature Page, Helsinn Healthcare SA

Medical Expert:

[redacted] 6 DEC 2017
(Date)

Study Coordinator:

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[redacted] 4 DEC 2017
(Date)
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(Date)
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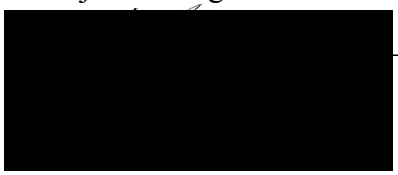
Medical Writer:

[redacted] 4 Dec 2017
(Date)
Senior Director, Clinical Research & Strategy

Signature Page, George Clinical Inc.

Project Manager:



05 Dec 2017
(Date)

Signature Page, PSI

Project Manager: [redacted] 06-Dec-2017

(Date)

Project Manager

Signature Page, Study Site Investigator

Study Title

A multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group phase 3b study to assess the safety and to describe the efficacy of IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) compared to oral netupitant/palonosetron (300 mg/0.5 mg) combination (Akynzeo®) for the prevention of chemotherapy-induced nausea and vomiting in initial and repeated cycles of anthracycline-cyclophosphamide (AC) chemotherapy in women with breast cancer.

Study Number NEPA-17-05

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, George Clinical Inc. and PSI CRO AG concerning this trial will be kept in the strictest confidence.

_____ _____

(Signature) (Date)

Printed Name:

Institution:

TABLE OF CONTENTS

GENERAL INFORMATION

Sponsor	Helsinn Healthcare SA Via Pian Scairolo 9 6912 Lugano, Switzerland Phone: +41 91 985 21 21 Fax: +41 91 985 21 22
CROs	**US Region:** George Clinical Inc. 6555 Quince, Suite 503 Memphis, TN 38119 Phone: +1 901.259.0888 Fax: +1 901.259.8276 **Europe:** PSI CRO AG Baarerstrasse 113a 6300 Zug, Switzerland Phone: +41 41 228 10 00 Fax: +41 41 228 10 99
24h-Contact for Serious Adverse Events (SAEs)	E-mail address for incoming SAE reports: SafetyDesk@psi-cro.com
Drug Safety Officer	**Helsinn:** [redacted] Helsinn Healthcare SA Phone: [redacted] Fax: [redacted] [redacted] (copies to drug-safety@helsinn.com) **CRO**: **US region:** [redacted] **Europe:** [redacted]

Medical Expert	**Helsinn:** [redacted]
Study Project Manager	**Helsinn:** [redacted] **CROs:** **US Region:** [redacted] **Europe:** [redacted]
Statistics	**Helsinn:** [redacted] **CRO:** [redacted]

Data Management	**Helsinn:** [redacted] **CRO:** [redacted]
Quality Assurance	**Helsinn:** [redacted] **CROs:** [redacted]
Clinical Study Supplies Packaging and Labeling	Catalent Germany Schorndorf GmbH Steinbeisstr. 1-2 D-73614 Schorndorf, Germany
IWRS Provider	Veracity Logic, LLC 11312 US 15 501 Hwy North Chapel Hill, NC 27517 Phone: +1 919.636.0655

EDC Provider	OmniComm (TrialMaster) 2101 West Commerical Blvd. Suite 3500 Fort Lauderdale, FL 33309 Phone: +1 877.468.6332

STUDY SYNOPSIS

Study Title	A multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group phase 3b study to assess the safety and to describe the efficacy of IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) compared to oral netupitant/palonosetron (300 mg/0.5 mg) combination (Akynzeo®) for the prevention of chemotherapy-induced nausea and vomiting in initial and repeated cycles of anthracycline-cyclophosphamide (AC) chemotherapy in women with breast cancer
Study Number	NEPA-17-05
Sponsor	Helsinn Healthcare SA, Via Pian Scairolo 9, 6912 Lugano, Switzerland
Countries and Sites	Approximately 50 sites in the US and approximately 30 sites distributed in Russia, Ukraine, and Georgia. If needed, additional sites and countries may be involved as well.
Clinical Phase	Phase 3b
Indication	Prevention of nausea and vomiting associated with Anthracycline-Cyclophosphamide (AC) based emetogenic cancer chemotherapy.
Study Design	Multicenter, randomized, double-blind, double-dummy, parallel group, stratified study assessing the safety and describing the efficacy of a single dose of intraveneous (IV) fosnetupitant/palonosetron (260 mg/0.25 mg) infusion [test] versus oral netupitant/palonosetron (300 mg/0.5 mg) combination [control]; each administered with oral dexamethasone prior to initial and repeated cycles of AC chemotherapy in female breast cancer patients.
Objectives	Primary: To evaluate the safety and tolerability of a single IV dose of fosnetupitant/palonosetron (260 mg/0.25 mg) combination administered as a 30-minute IV infusion with oral dexamethasone on Day 1 for the prevention of AC chemotherapy-induced nausea and vomiting in initial and repeated cycles. Secondary: To describe the efficacy of a single IV dose of fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) administered as a 30-minute IV infusion versus a single oral dose of netupitant/palonosetron (300 mg/0.5 mg) combination (oral NEPA FDC)

	administered as one capsule, during the acute (0-24 hours), delayed (>24-120 hours) and overall (0-120 hours) phases of initial and repeated cycles of AC chemotherapy. Exploratory: To evaluate the impact on economics and resource utilization through collection of Health Economics Outcomes Research (HEOR) parameters in initial and repeated cycles of AC chemotherapy.
Treatment Groups	Group 1 / Test group – intravenous fosnetupitant/ palonosetron (260 mg/0.25 mg) fixed-dose combination, administered as a 30-minute infusion of a 50 mL solution, on Day 1 of each cycle. Group 2 / Control group – oral netupitant/palonosetron (300 mg/0.50 mg) fixed-dose combination on Day 1 of each cycle. Oral dexamethasone will be administered on Day 1 of each cycle (12 mg) to both test and control groups.
Drug Administration	The administration of test and control drugs will be double-blinded. Oral netupitant/palonosetron (300 mg/0.50 mg) fixed-dose combination capsule (or matching placebo capsule) will be administered on Day 1 of each cycle, 60 minutes prior to the start of AC chemotherapy. The 30-minute IV fosnetupitant/palonosetron (260 mg/0.25 mg) fixed-dose combination infusion (or matching placebo infusion) will start 30 minutes prior to the start of the AC chemotherapy on Day 1 of each cycle. The IV infusion will be completed before starting chemotherapy administration. Administration of dexamethasone will not be blinded as the dosage and schedule are identical in both treatment groups, i.e., 12 mg on Day 1 of each cycle as a unique dose. On Day 1 of each cycle, oral dexamethasone will be taken 30 minutes prior to the start of the AC chemotherapy, immediately before the start of the 30-minute IV fosnetupitant/palonosetron (260 mg/0.25 mg) fixed-dose combination or placebo infusion.
Study Duration	Each randomized patient is planned to participate in a maximum of 4 consecutive chemotherapy cycles assessed in this study. A total of 400 patients will be randomized. Study drug assignment for Cycles 2 to 4 will be closed 7 days after

	the last (400th) patient is randomized, in order to permit patients already screened for a subsequent study cycle to be administered study drug. Patients still participating in the study at this time should complete their current cycle and will not be allowed to enter in a subsequent cycle. For each cycle, patients will undergo a screening visit (Visit 1) up to 7 days (up to 14 days for Cycle 1 only) before study drug administration (Day 1; Visit 2). After receiving a single dose of active treatment on Day 1, patients will enter an efficacy evaluation period of 120 hours and then return to the clinical site on Day 6 (+2) for Visit 3. Patients will undergo a follow-up visit or telephone call (Visit 4) either on Day 15 (+3 days) or Day 22 (±3 days) depending on the next chemotherapy cycle schedule (this Visit 4 will be considered as the end of each "Study Cycle"). Visit 4, or the corresponding telephone contact, either on Day 15 (+3 days) or on Day 22 (±3 days) is to be performed prior to administering the chemotherapy relevant to the next cycle and prior to any further moderately or highly emetogenic chemotherapeutic treatment administration. Total number of visits per patient: For each cycle, there will be a maximum of 4 visits or 3 visits plus 1 telephone contact. For all cycles, the screening visit and the study drug administration visit can be performed on the same day. The screening visit of a subsequent cycle can also coincide with the follow-up visit of the previous cycle. If all these visits are merged, Visit 4 of the previous cycle as well as Visit 1 and Visit 2 of the next cycle are all three performed on the same day. Total number of cycles per patient: Each patient may participate in a maximum of 4 consecutive chemotherapy cycles, as long as they continue to fulfill the inclusion and exclusion criteria for the repeated cycles and as long as the study remains open. Maximum total study duration per patient is approximately 14 weeks. This maximum total study duration per patient is based on the assumption that the patient participates in 4 consecutive study cycles (maximum number of cycles allowed in the study) with 21 days interval between the Day 1 of two consecutive cycles, and that follow-up visits of one cycle coincide with screening visits of the subsequent cycle. A minimum of 14 days and maximum of 35 days is allowed between the Day 1 of two consecutive cycles.

Number of Patients	A total of 400 patients will be randomized according to a 1:1 randomization ratio, stratified by region (US, non-US) and age class (age < 55 years, age ≥ 55 years).
Target Study Population	Adult female patients naïve to moderately or highly emetogenic antineoplastic agents with a diagnosis of breast cancer requiring treatment with an AC based chemotherapy regimen on Day 1.
Inclusion Criteria	Cycle 1**:** The following inclusion criteria must be checked prior to inclusion at Cycle 1: 1. Patient read, understood and signed the written informed consent before any study related activity, agreeing to participate in the study and to comply with study requirements. 2. Female patient ≥ 18 years of age. 3. Histologically or cytologically confirmed breast cancer, including recurrent or metastatic. 4. Naïve to moderately or highly emetogenic antineoplastic agents (see Appendix 1). 5. Scheduled to receive at least 4 consecutive cycles of an AC combination regimen. Notes: a) additional not emetogenic, minimally or low emetogenic antineoplastic agents (see protocol Appendix 1) are permitted at any time after start of AC combination on Day 1. b) additional highly or moderately emetogenic antineoplastic agents (see protocol Appendix 1) are only allowed on Day 1 after the start of AC combination, provided their administration is completed within 6 hours from the start of the AC combination administration. 6. ECOG Performance Status of 0 or 1. 7. Patient shall be: a) of non-childbearing potential or b) of childbearing potential using reliable contraceptive measures and having a negative urine pregnancy test within 24 hours prior to dose of investigational product.

	Notes: a) Female patients of non-childberaring potential are defined as being in post-menopausal state since at least 1 year; or having documented surgical sterilization or hysterectomy at least 3 months before study participation. b) Reliable contraceptive measures include implants, injectables, combined oral contraceptives, intrauterine devices, vasectomized partner or complete (long term) sexual abstinence; 8. Hematologic and metabolic status adequate for receiving a cycle of AC chemotherapy based on investigator's assessment. 9. If the patient has a known hepatic or renal impairment, she may be enrolled in the study at the discretion of the Investigator. 10. Able to read, understand, follow the study procedure and complete the patient diary. All inclusion criteria will be checked at screening visit (Visit 1 of Cycle 1); inclusion criteria #7 will be re-checked at Day 1 (Visit 2). <u>Cycles 2 to 4:</u> The following inclusion criteria must be checked prior to inclusion at each repeated cycle: 1. Participation in the study during the next cycle of chemotherapy is considered appropriate by the Investigator and does not pose unwarranted risk to the patient. 2. Scheduled to receive an AC chemotherapy regimen or AC chemotherapy together with other chemotherapies as defined in Inclusion criterion #5 for Cycle 1. 3. Patient shall be: a) of non-childbearing potential or b) of childbearing potential using reliable contraceptive measures and having a negative urine pregnancy test within 24 hours prior to dosing of investigational product. 4. Adequate hematologic and metabolic status for receiving a cycle of AC chemotherapy according to the Investigator's opinion. All inclusion criteria will be checked at screening visit

	(Visit 1); inclusion criterion #3 will be re-checked at Day 1 (Visit 2).
Exclusion Criteria	Cycle 1: The following exclusion criteria must be checked prior to inclusion at Cycle 1: 1. Lactating patient. 2. Current use of illicit drugs or current evidence of alcohol abuse. 3. Scheduled to receive moderately or highly emetogenic antineoplastic agent (see protocol Appendix 1) in addition to the AC regimen, from 6 hours after the start of the AC chemotherapy on Day 1 and up to Day 1 of Cycle 2. 4. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of AC chemotherapy administration on Day 1 or between Days 1 to 5, inclusive. 5. Any vomiting, retching, or nausea (grade ≥ 1 as defined by National Cancer Institute) within 24 hours prior to the start of AC chemotherapy administration on Day 1. 6. Symptomatic primary or metastatic central nervous system (CNS) malignancy. 7. Active peptic ulcer disease, gastrointestinal obstruction, increased intracranial pressure, hypercalcemia, an active infection or any illness or medical conditions (other than malignancy) that, in the opinion of the Investigator, may confound the results of the study, represent another potential etiology for emesis and nausea (other than chemotherapy-induced nausea and vomiting [CINV]) or pose unwarranted risks in administering the study drugs to the patient. 8. Known hypersensitivity or contraindication to 5 hydroxytryptamine type 3 (5-HT3) receptor antagonists (e.g., palonosetron, ondansetron, granisetron, dolasetron, tropisetron, ramosetron), to dexamethasone, or to neurokinin-1 (NK1) receptor antagonists (e.g., aprepitant, rolapitant). 9. Known contraindication to the IV administration of 50 mL 5% glucose solution.

	10. Participation in a previous clinical trial involving IV fosnetupitant or oral netupitant administered alone or in combination with palonosetron. 11. Any investigational drugs taken within 4 weeks prior to Day 1, and/or is scheduled to receive any investigational drug (other than those planned by the study protocol) during the present study. 12. Systemic corticosteroid therapy within 72 hours prior to the start of AC chemotherapy administration on Day 1, except the dexamethasone provided as additional study drug. However, topical and inhaled corticosteroids are permitted. 13. Scheduled to receive bone marrow transplantation and/or stem cell rescue therapy during the study participation. 14. Other than as administered as part of the study protocol, any medication with known or potential antiemetic activity within 24 hours prior to the start of AC chemotherapy administration on Day 1, including: • 5-HT3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron, tropisetron, ramosetron, palonosetron) • NK1 receptor antagonists (e.g., aprepitant, fosaprepitant, rolapitant or any other new drug of this class) • benzamides (e.g., metoclopramide, alizapride) • phenothiazines (e.g., prochlorperazine, promethazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine) • benzodiazepines (except if the subject is receiving such medication for sleep or anxiety and has been on a stable dose for at least seven days prior to Day 1). • butyrophenones (e.g., haloperidol, droperidol) • anticholinergics (e.g., scopolamine, with the exception of inhaled anticholinergics for respiratory disorders, e.g., ipratropium bromide) • antihistamines (e.g., cyclizine, hydroxyzine, diphenhydramine, chlorpheniramine) • domperidone • mirtazapine • olanzapine • prescribed cannabinoids (e.g.,

	tetrahydrocannabinol or nabilone) • Over The Counter (OTC) antiemetics, OTC cold or OTC allergy medications. 15. Scheduled to receive any strong or moderate inhibitor of CYP3A4 (see protocol Appendix 3) during the efficacy assessment period (Day 1 to Day 5, inclusive) or its intake within 1 week prior to Day 1. 16. Scheduled to receive any CYP3A4 inducer (see protocol Appendix 3) during the efficacy assessment period (Day 1 to Day 5, inclusive) or its intake within 4 weeks prior to Day 1, with the exception of corticosteroids (for which exclusion criterion #12 applies). 17. History or predisposition to cardiac conduction abnormalities, except for incomplete right bundle branch block. 18. History of risk factors for Torsades de Pointes (heart failure, hypokalemia, family history of Long QT Syndrome). 19. Severe or uncontrolled cardiovascular diseases, including myocardial infarction within 3 months prior to Day 1, unstable angina pectoris, significant valvular or pericardial disease, history of ventricular tachycardia, symptomatic Congestive Heart Failure (CHF) New York Heart Association (NYHA) class III-IV, and severe uncontrolled arterial hypertension. All exclusion criteria with the exception of criteria #5, #12, and #14 will be checked at screening visit (Visit 1). Exclusion criteria #5, #12, and #14 will be checked at Day 1 (Visit 2) only. Exclusion criteria #3, #4, #7, #11, #13, #15, and #16 need to be re-checked at Day 1 (Visit 2). <u>Cycles 2 to 4:</u> The following exclusion criteria must be checked prior to inclusion at each repeated cycle: 1. Scheduled to receive moderately or highly emetogenic antineoplastic agent (see protocol Appendix 1) in addition to the AC regimen, from 6 hours after the start of the AC chemotherapy on Day 1 of current cycle and up to Day 1 of the next cycle.

	2. Active infection or uncontrolled disease that may pose unwarranted risks in administering the study drugs to the patient. 3. Started any of the prohibited medications (see protocol Section 5.14). 4. Any vomiting, retching, or nausea (grade ≥ 1 as defined by National Cancer Institute) within 24 hours prior to the start of AC chemotherapy administration on Day 1. 5. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of AC chemotherapy administration on Day 1 or between Days 1 to 5. 6. Symptomatic primary or metastatic CNS malignancy. 7. Any illness or medical condition that, in the opinion of the investigator, may confound the results of the study or pose unwarranted risks in administering the investigational product or dexamethasone to the patient. All exclusion criteria, with exception of criterion #4, will be checked at screening visit (Visit 1). Exclusion criterion #4 will be checked at Day 1 (Visit 2) only. Exclusion criteria #2, #3 and #5 need to be re-checked at Day 1 (Visit 2).
Efficacy Assessments	Time-related efficacy study parameters assessment will start at "time 0" defined as the start time of the AC chemotherapy administration on Day 1 of each cycle. Efficacy parameters will be evaluated at each cycle in the acute, delayed and overall phases (time intervals 0 to 24 hours, >24 to 120 hours and 0 to 120 hours after the start of AC chemotherapy, respectively), if not otherwise noted. The efficacy endpoints are defined as follows: • The proportion of patients with CR (defined as no emetic episodes and no rescue medication) during the acute, delayed and overall phases; • the proportion of patients with no emetic episodes during the acute, delayed and overall phases; • the proportion of patients with no rescue medication during the acute, delayed and overall phases; • the proportion of patients with no nausea (defined as maximum nausea intensity on a 100-mm visual analog scale (VAS) < 5mm) during the acute, delayed and overall phases;

	• the proportion of patients with no significant nausea (defined as maximum nausea intensity on a 100-mm VAS < 25mm) during the acute, delayed and overall phases; • the severity of nausea (defined as the maximum nausea intensity on the 100-mm VAS) in the acute, delayed and overall phases; • the proportion of patients with no impact on daily life (NIDL) activities in the overall phase of Cycle 1 and 2, only as assessed by the Functional Living Index-Emesis (FLIE) questionnaire. NIDL is defined as a score greater than 108 points, 54 points, and 6 points for total FLIE score, domain score and single item score, respectively; • the domain (nausea and vomiting) FLIE scores and the total FLIE score in the overall phase of Cycle 1 and 2, only.
Safety Assessments	The following safety assessments will be obtained in each Study Cycle: physical examination (PE), vital signs, laboratory tests and adverse events (AEs) assessment.
HEOR Assessments	The following exploratory HEOR assessments will be obtained: • Emergency Department (ED), and Inpatient Admissions (IP) and length of stay (LOS) • Lost work time and productivity assessed by the Work Productivity and Activity Impairment (WPAI) Questionnaire (Cycles 1 and 2 only) • Disruptions in initiation and dosing of intended next cycle of chemotherapy Additional data collected from patient diary or electronic Case Report Forms (eCRFs) may also be used for HEOR-related analysis. All parameters of interest, endpoints and analysis methods will be specified in a separate Health Economics Analysis Plan.

Efficacy Analysis	Analysis Population Population for efficacy analyses is defined as follows: The **Full Analysis Set (FAS)** includes all randomized patients who received the AC chemotherapy regimen and active study drug (including partial infusion). Following the intent-to-treat principle, patients will be assigned to the treatment group to which they were randomized. FAS will be used for demography, other baseline characteristics and all descriptive efficacy analyses. Efficacy Analysis At each cycle, for each phase (acute, delayed, and overall), numbers and proportions (including 95% confidence interval [CI]) of patients with CR, with no emetic episodes, with no rescue medication, with no nausea, and with no significant nausea will be descriptively summarized. Difference between groups in response rate and 95% CI will be presented without strata adjustment using the Newcombe-Wilson method and with strata adjustment using the Cochran-Mantel-Haenszel (CMH) method with region and age class as strata. The severity of nausea will be descriptively summarized including difference between groups. For Cycles 1 and 2, numbers and proportions of patients with NIDL for total FLIE score and for domain scores in the overall phase will be descriptively summarized and difference between treatment groups presented without strata adjustment and with strata adjustment using the CMH method as mentioned above.The domain (nausea and vomiting) FLIE scores and the total FLIE score will be descriptively summarized including difference between groups.
Safety Analysis	Analysis Population Population for safety analyses is defined as follows: The **Safety population** includes all patients who received active study drug (including partial infusion). 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.

	Safety Analysis Treatment-emergent AEs (TEAEs) will be listed and summarized by frequency tables. Summaries will be made with respect to the number and proportion of patients with events and the total number of events. A similar summary will be presented for Cycle 1 only. In addition, TEAEs of special interest, i.e. the ones related to local tolerability (e.g. injection site reaction, pain at injection site, thrombophlebitis) will be presented for each cycle. Vital signs will be summarized using descriptive statistics for observed values, change from baseline, and change from pre-dose assessment, in addition to being listed. Proportion of laboratory values below, within and above normal range will be presented by frequency table for each timepoint. Shift table (below, within and above normal range) comparing baseline assessment with on-treatment assessment and comparing pre-dose assessment with Visit 3 assessment of each cycle will also be presented.
HEOR Analysis	The HEOR analysis will be managed and conducted separately. Relevant patient data and results will be presented in a separate report. Further details (including detailed description of HEOR endpoints and analyses) will be outlined in the Health Economics Analysis Plan.

FLOW CHART

Study Phase	*Study Cycle (Cycle 1 / Repeated Cycles)*			
Procedure/assessment	Screening Day -14 to 1 days (Cycle 1 only) / -7 to Day 1 (Cycles 2-4)[a]	Day 1	Day 6 (+2 days) [b]	On Day 15 (+3 days) OR Day 22 (+/-3 days) [c]
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4 (Follow-up)**
Informed consent	X[d]			
Inclusion / exclusion criteria [e]	X	X		
Demography	X[d]			
Alcohol, tobacco and illicit drugs consumption	X			
Reproductive status	X			
Medical history (including current cancer history, and surgery)	X[d]			
ECOG performance status	X			
Urine pregnancy test [f]	X	X		
Prior and concomitant medications	X	X	X	X
Physical examination [g]	X		X	
Vital signs [h]	X	X	X	
Height and weight [i]		X		
Blood chemistry[j]	X		X	
Hematology[j]	X		X	
Pt. no assignment by IWRS	X[d]			
Randomization		X[d]		
Study drug assignment through IWRS		X		
Study drugs administration		X		
Dexamethasone administration [k]		X		
AC chemotherapy		X		
Patient Diary [l]		X	X	
FLIE questionnaire [m]		X	X	
WPAI questionnaire for HEOR[n]		X	X	
ED/Hospitalization information for HEOR [o]				X
Chemotherapy information for HEOR [p]		X		
Adverse events [q]	X	X	X	X

a) Screening activities for Cycle 1 may be performed or completed between Day -14 and Day 1, included. In repeated cycles (i.e., cycles no. 2, 3 or 4), Visit 1 may be performed from Day -7 up to study Day 1 inclusive. For all cycles, Visit 1 and Visit 2 may occur on the same day (on study Day 1). In that case, the assessments planned at both Visit 1 and Visit 2 have to be performed only once.

b) Visit 3 (Day 6 [+ 2 days]) is to be scheduled on Day 6, not earlier than 120 hours after start of AC chemotherapy administration on Day 1. If Day 6 is a holiday or a weekend day, or in case Visit 3 cannot be performed on Day 6 after the end of the 120 hours period for any reason, Visit 3 may be scheduled within the two forthcoming days.

c) Visit 4, follow-up visit, either as on-site visit or telephone contact, is to be performed either on Day 15 (+3 days) or on Day 22 (±3 days) depending on the next chemotherapy cycle schedule. The patient's follow-up visit or contact is to be performed prior to administering the chemotherapy relevant to the next cycle and prior to any further moderately or highly emetogenic chemotherapeutic treatment administration to the patient. Visit 4 of a previous cycle, as well as Visit 1 and Visit 2 of the next cycle, can all coincide and be performed on the same day.

d) Only at Cycle 1

e) Some inclusion / exclusion criteria are to be verified at Screening visit (Visit 1) and confirmed at the Day 1 visit (Visit 2); if Visit 1 and Visit 2 are performed on the same day (Day 1), a unique assessment of these criteria is sufficient; please refer to inclusion / exclusion criteria section for details.

f) To be performed for females of childbearing potential within 24 hours prior to the IMP administration at each cycle (oral netupitant/palonosetron combination or placebo capsule) on Day 1. If the screening visit urine pregnancy test has been done within the 24 hours before the IMP administration, no urine pregnancy test is to be performed at Visit 2 (Day 1).

g) Complete PE (general appearance, head, eyes, ears, nose, throat, skin, neck, lungs, cardiovascular, breast, lymph nodes, abdomen, musculoskeletal and neurological) to be performed at Visit 1 and Visit 3 of each cycle. At Visit 3 and at subsequent cycles, only the general question "Was PE performed?" will be asked on the eCRF. Any new or worsening of pathological findings noted since previous examination should be reported on the Adverse Event eCRF form.

h) Vital signs assessments include: pulse rate, systolic and diastolic blood pressure at Visit 1 (screening), Visit 2 (on Day 1 at pre-dose, i.e., within 30 minutes before the oral netupitant/palonosetron combination or placebo capsule administration) and Visit 3 of each cycle. Pulse rate and systolic and diastolic blood pressure have to be measured after the patient has been in semi-supine position for at least 5 minutes.

i) Height has to be measured only at Visit 2 (Day 1) of Cycle 1. Weight has to be measured at Visit 2 (Day 1) of each cycle, and should occur prior to the start of the AC chemotherapy administration.

j) Local laboratories will be used for haematology and blood chemistry analysis throughout the study.

k) Patients will receive 12 mg dexamethasone on Day 1 of each cycle. Dexamethasone is to be administered 30 minutes prior to the start of the AC chemotherapy administration (immediately before IV NEPA FDC or placebo infusion).

l) The patient's diary, referring to the 0-120 hour period, will be distributed to the patients at the Day 1 Visit of each cycle. Patients will be asked to report date and time of onset of emetic episodes (episodes of retching or vomiting), date and time of intake of rescue medication, name of the rescue medication taken, and daily nausea intensity assessed by VAS on their diary. The patient's completed diary will be retrieved and checked by the Investigator or designated responsible person during study Visit 3 of each cycle.

m) FLIE questionnaire, referring to the 0-120 hour period, will be distributed to the patients at the Day 1 Visit, with explanations on how to perform the requested assessments; the patient's completed FLIE will be retrieved and checked by the Investigator or designated responsible person during study Visit 3. FLIE questionnaire will only be administered during Cycle 1 and Cycle 2.

n) The WPAI questionnaire, referring to the 0-120 hour period, will be distributed to the patient at the Day 1 Visit, with explanations on how to complete the questionnaire; the patient's completed WPAI will be retrieved and checked by the Investigator or designated responsible during study Visit 3. WPAI questionnaire will only be administered during Cycle 1 and Cycle 2.

o) Hospitalization information (including ED, IP and LOS, and initiation dates thereof), referring to the interval from Visit 2 (Day 1) through Visit 4 of each cycle, will be recorded.

p) Starting at Cycle 2 Visit 2 (Day 1), the Investigator will document if changes in chemotherapy administration from the previous cycle occurred and will note any delays in treatment for the current cycle.

q) Adverse events will be collected from Informed Consent signature until end of the study (completion/discontinuation), as a minimum. If the patient exit the study less than 15 days after last study drug administration, the patient should be followed-up for AE recording up to 15 days after last study drug administration. All non-resolved AEs (including SAEs) beyond this date will be documented on the eCRF as "ongoing". For SAE follow-up requirements, see Section 8.1.3.1.

LIST OF ABBREVIATIONS

5-HT_3	5-hydroxytryptamine type 3
AC	Anthracycline-Cyclophosphamide
ADL	Activities of Daily Living
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
ALT	Alanine Aminotransferase
AUC	Area Under the Curve
AST	Aspartate Aminotransferase
CHF	Congestive Heart Failure
CI	Confidence Interval
CINV	Chemotherapy-Induced Nausea and Vomiting
CL	Clearance
CLr	Renal Clearance
C_{max}	Maximum Plasma Concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
CR	Complete Response
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
EMA	European Medicine Agency
EU	European Union
FAS	Full Analysis Set

FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
FLIE	Functional Living Index-Emesis
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
HEC	Highly Emetogenic Chemotherapy
HEK	Human Embryonic Kidney
HEOR	Health Economics Outcomes Research
hERG	Human Ether-à-go-go-related Gene
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IKr	Delayed Rectifier Potassium Current
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IP	Inpatient Admission
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
kg	Kilogram
LOCF	Last Observation Carried Forward
LOS	Length of Stay
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MEC	Moderately Emetogenic Chemotherapy
min	Minute
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
NEPA	Netupitant and Palonosetron
NIDL	No Impact on Daily Life
NK_1	Neurokinin-1
NOEL	No Observed Effect Level

NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
OTC	Over The Counter
PALO	Palonosetron
PE	Physical Examination
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Events
t_{max}	Time to Maximum (Plasma) Concentration
US	United States of America
VAS	Visual Analog Scale
Vd	Volume of Distribution
WPAI	Work Productivity and Activity Impairment

1 INTRODUCTION AND RATIONALE

1.1 Background Information

Cancer chemotherapy is often associated with nausea and vomiting, which are among the most unpleasant and distressing subjective side effects [1, 2]. Chemotherapy-induced nausea and vomiting (CINV) reduces patient's health related quality of life and may cause non-compliance or refusal of potentially life-saving chemotherapeutic regimens [2]. The severity and pattern of nausea and vomiting induced by a chemotherapeutic regimen depend on the agents used and the doses employed [1]. In this respect, chemotherapeutic regimens are classified as highly, moderately, low, and minimally emetogenic [1].

Palonosetron hydrochloride is a specific 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist used to prevent CINV when subjects receive moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC), and is a known chemical entity currently registered in the oral and intravenous (IV) forms in several countries [3, 4, 5].

In the US, in July 2003, the Food and Drug Administration (FDA) approved palonosetron 0.25 mg IV given as a 30-second bolus, for the prevention of acute CINV associated with highly or moderately emetogenic chemotherapy and for prevention of delayed CINV associated with MEC (initial and repeat courses). In Europe, in March 2005, the European Medicine Agency (EMA) approved the product via the Centralized Procedure for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy and moderately emetogenic cancer chemotherapy

The oral palonosetron formulation (0.50 mg capsule) is approved in the US (August 2008) and in the EU (January 2010) for the prevention of moderately emetogenic CINV.

At present, the product is registered in more than 70 countries with different trademarks (Aloxi®, Onicit®, Paloxi®).

Netupitant is a new, highly efficient, selective neurokinin-1 (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), and is a new chemical entity. [6]

Helsinn developed an oral combination (NEPA 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-gelatin capsule to be administered as a single dose 1 hour prior to chemotherapy.

In the US oral NEPA FDC (Akynzeo®) was approved in October 2014, for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of chemotherapy, including but not limited to HEC [6].

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. [7]

Since netupitant is not water-soluble and, as such, early parenteral formulations did not show a satisfactory local tolerability profile, the Sponsor developed fosnetupitant, a water-soluble phosphorylated pro-drug of netupitant, which is rapidly converted to netupitant in vivo following IV administration. Fosnetupitant proved to overcome tolerability issues that were observed with former IV netupitant formulations [6]. Fosnetupitant was administered as a single dose by IV route at dosages of 19.5 mg up to 390 mg to a total of 179 healthy male and female volunteers, showing a good safety profile.

An IV formulation of fosnetupitant/palonosetron, IV NEPA FDC, was developed [8]. The fosnetupitant component dose in this formulation is 260 mg, which showed to be equivalent in exposure (Area Under the Curve, AUC) to the netupitant dose used in oral NEPA FDC (300 mg netupitant) (study PNET-12-23 [9]). The selected dose for the palonosetron component in the IV NEPA FDC is 0.25 mg, i.e., the registered dose of Aloxi® IV.

Helsinn recently completed a phase 3, active-controlled, double-blind, randomized, multi-cycle safety study with IV NEPA FDC versus oral NEPA FDC in more than 400 cancer patients mainly receiving HEC. Study patients were allowed to receive the study drug in up to 4 consecutive repeated chemotherapy cycles. Study results confirmed the good safety profile and the satisfactory antiemetic efficacy of IV NEPA FDC in cancer patients (Study NEPA-15-18, [13]).

The sponsor also recently completed an open label pharmacokinetic (PK) study in cancer patients treated with IV NEPA FDC as a 30-minute infusion and receiving cisplatin based HEC (Study NEPA-15-19, [10]). The PK results obtained in cancer patients confirmed the rapid conversion of fosnetupitant into netupitant after IV administration previously shown in healthy volunteers. Study results in cancer patients also show that an IV dose of 260 mg fosnetupitant/0.25 mg palonosetron yields a netupitant exposure equivalent to that of 300 mg netupitant oral dose, previously evidenced in healthy volunteers. With regards to palonosetron, the PK profile was superimposable to that observed in a previous PK study in healthy volunteers receiving 0.25 mg palonosetron IV bolus (Study PALO-03-05), with the obvious exception of maximum concentration (C_{max}) which was lower after 30-min infusion as compared to the IV bolus.

NEPA-17-05 study will evaluate the safety and describe the efficacy of IV NEPA FDC fosnetupitant/palonosetron (260 mg/0.25 mg) combination, given as a 30-minute infusion compared with oral netupitant/palonosetron (300 mg/0.5 mg) combination (oral NEPA FDC) in female breast cancer patients receiving AC chemotherapy, allowing to complete the information on the antiemetic efficacy and safety of IV NEPA FDC in the AC chemotherapy setting.

In addition to the described oral or IV combination, study patients will also receive a regimen of oral dexamethasone as part of the anti-emetic treatment.

1.2 Pre-clinical and Clinical Data of Palonosetron

1.2.1 Pre-clinical Data

As described above, palonosetron is a well-known chemical entity that has been on the world market for more than 12 years as an IV formulation and for more than 5 years as an oral agent. For pre-clinical data on palonosetron, reference is made to the dedicated Investigator's Brochure [4].

1.2.2 Summary of Phase 1 Clinical Data (Human Pharmacokinetics)

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 of approximately 40 hours 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 plasma 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 subjects and in 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 hours. [4]

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 has 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. [4]

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 IV administration. [4]

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 hours 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 is 53±29 mL/min. The low total body clearance and large volume of distribution results in a terminal elimination half-life of approximately 40 hours, which is substantially longer than that of other 5-HT$_3$ antagonists, i.e., ondansetron (4-6 hours), granisetron (5-8 hours), tropisetron (7 hours) and dolasetron (7 hours).Ten percent of patients revealed a mean terminal elimination half-life greater than 100 hours. 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 hours and between 192 and 216 hours post-dose in plasma and urine, respectively. Quantifiable concentrations of M9 metabolite were reported for all subjects until at least 24 hours and between 120 and 144 hours post-dose in plasma and urine, respectively. [4]

1.2.3 Clinical Data

In clinical studies, adverse events (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 active comparators [4]. 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 postoperative nausea and vomiting.

For further information about palonosetron, including PK, pharmacodynamics, clinical efficacy and safety, please refer to the current edition of the Investigator's Brochure [4].

1.3 Pre-clinical and Clinical Data of Fosnetupitant and Netupitant

Fosnetupitant is the water-soluble phosphorylated pro-drug of netupitant. Fosnetupitant is rapidly converted to netupitant in vivo following IV administration. Fosnetupitant proved to overcome tolerability issues that were observed with former IV netupitant formulations and was therefore used as the "netupitant component" in the IV netupitant/palonosetron combination formulation. [8]

1.3.1 *Pre-clinical Data*

1.3.1.1 *Fosnetupitant*

A pre-clinical development program for fosnetupitant, in addition to specific pre-clinical studies with the combination of fosnetupitant and palonosetron, has been performed.

Safety Pharmacology

Central nervous system

An Irwin test study in rats (PNET-12-01) was performed to evaluate the possible effects of fosnetupitant on general behavior parameters. A single IV administration of fosnetupitant at 13.16 and 39.47 mg/kg corresponding to 10 and 30 mg/kg of netupitant, respectively, did not induce any changes in behavioral, neurological or autonomic functions of rats. No clinical signs were observed on the day of dosing or during the subsequent 6-day observation period in animals of low and mid-dose groups. Pro-convulsant (PNET-13-69) and anticonvulsant (PNET-13-70) activity were also assessed in rats with fosnetupitant. Fosnetupitant did not show any pro-convulsant nor anticonvulsant activity up to 79 mg/kg/day.

Cardiovascular system

The effects of fosnetupitant on the delayed rectifier potassium current (IKr) encoded by human ether-à-go-go-related gene (hERG) were studied at a stimulation frequency of 6 pulses/min (0.1 Hz) in stably transfected Human Embryonic Kidney (HEK293) cells (PNET-12-06). A vehicle group (1 period with extracellular solution) was included in the study for comparison and terfenadine (1 µM) was used as reference substance. The results suggest that fosnetupitant up to 30 µM would possess no liability for prolonging QT interval (QT) in this model.

A study assessing the cardiovascular functions in dogs (PNET-12-35) following 2-week IV fosnetupitant administration up to 13.2 mg/kg/day showed no effects on PR-, QT-, ST-, QTcV-, QTcF -, or RR- intervals or QRS complex duration.

Respiratory, Renal, Urinary, and Gastrointestinal Systems

Specific studies were planned and performed to evaluate possible effects on respiratory, renal, urinary, and gastrointestinal systems for fosnetupitant. No changes of toxicological relevance were detected in renal function at 13.2 mg/kg fosnetupitant dose level. Transient decrease in urine volume output and moderate significant decrease of electrolyte excretion were observed at 39.5 and 79.0 mg/kg (PNET-13-34). No changes of toxicological significance in respiratory parameters were observed with fosnetupitant up to 79.2 mg/kg (PNET-14-19). No effects on gastrointestinal motility (PNET-13-67) were observed in rats at doses up to 39.5 mg/kg. A statistically significant decrease in GI transit of the charcoal meal versus vehicle control was noted at 79.0 mg/kg. [8]

Toxicology

Several repeat dose toxicity studies with fosnetupitant were performed in rats and dogs following IV administration up to 4 weeks.

In the 2-week study, the repeated IV administration of fosnetupitant to rats (PNET-11-21) at the doses of 3.95, 13.16, and 39.47 mg/kg/day (equivalent to 3, 10, and 30 mg of netupitant, respectively) resulted in slight toxic effects mainly affecting the liver of the rats receiving the highest dose. These effects were reversible after a 2-week recovery period.

In the 4-week IV toxicity study in rats (PNET-13-18) at the same doses of the 2-week study, the repeated administration of fosnetupitant resulted in a liver centrilobular hypertrophy in high dose and mid-dose groups. These changes correlated with increased liver weight. No significant differences were observed in liver weights after the 2 week recovery period. Liver changes observed were not associated with any other alteration and were not considered as adverse. On the basis of the results obtained in the study, the dose level of 13.16 mg/kg/day was considered as the No Observed Effect Level (NOEL) for systemic and local effects, and the dose level of 39.47 mg/kg/day was defined as the No Observed Adverse Effect Level (NOAEL) for local effects.

In a 2-week study in dogs, the repeated daily IV administration of fosnetupitant (PNET-11-22) at the same doses resulted in no toxic effects after 14 days of treatment. No statistically significant increments in QTc were observed.

In the 4-week IV toxicity study in dogs (PNET-13-27) at dose levels 1.316, 3.95 and 13.16 mg/kg/day, there were no changes in electrocardiographic parameters, hematology, coagulation, clinical chemistry or urinalysis. Decreases in body weight were noted in both sexes at the high-dose level during the dosing phase, associated with a decrease in food consumption. However, these changes were not considered as adverse and showed reversibility after the 2-week recovery period. At the microscopic examination, changes were noted in thymus of the high-dose group, in addition, minimal increases in multifocal necrotic lymphocytes were noted in the same group.

No changes were noted in thymus weight and at microscopic observations after a 2-week treatment-free period. The NOAEL was 13.16 mg/kg/day for systemic and local effects and the NOEL was 3.95 mg/kg/day.

Fosnetupitant did not show mutagenic activity in the Ames test (PNET-12-04). In the Chromosome aberrations test no structural aberrations were observed in human lymphocytes (PNET-12-05).

The assessment of the ability of fosnetupitant to induce chromosomal damage was performed in the micronucleus test in rats following IV administration up to 118.4 mg/kg/day (PNET-13-49). The study showed no clastogenic effect and no micronuclei in polychromatic erythrocytes.

In general, studies showed that fosnetupitant had no hemolytic effect and showed a good tolerability profile when injected IV in rats and dogs daily for up to 14 days.

Pharmacokinetics and metabolism in animals

In rats and dogs, fosnetupitant is rapidly converted into netupitant after IV administration. *In vitro* metabolic stability data in lung, kidney, intestine and liver S9 and in vivo PK data suggest that the hydrolysis of fosnetupitant to netupitant occurs in multiple tissues and not only in the liver. The exposure (AUC) of netupitant in rats after equimolar administration of IV fosnetupitant and netupitant was comparable, which indicates a 1:1 conversion.

Three major circulating metabolites of netupitant have been identified: M1 (desmethyl derivative), M2 (N-oxide derivative), and M3 (OH-methyl derivative). In the 2 preclinical

species dosed IV with fosnetupitant, the exposure to netupitant and to the 3 main circulating metabolites, M1, M2 and M3, are comparable with the exposures measured after direct IV or oral administration of netupitant following single and multiple doses. In the 14-day toxicity study in rats (PNET-11-21), females seemed to be more exposed than male rats suggesting that the kinetics of the drug may be gender dependent. An accumulation of metabolite M1 and, in minor proportion, of metabolites M2 and M3 was observed. A 4th metabolite (M4) has been recently detected and studies aiming at better characterization of M4 showed that it is present in much smaller proportion than the other 3 metabolites.

The high fosnetupitant in vivo clearance in rats and dogs, which is higher than hepatic blood flow, and the high to moderate volume of distribution suggest that the fast hydrolysis of fosnetupitant to netupitant occurs in multiple tissues and not only in the liver. The subsequent in vivo elimination of netupitant is due to biliary excretion and hepatic metabolism (mainly mediated by cytochrome P450[CYP]3A4 and lesser extent by CYP2C9 and CYP2D6 in humans). Possible in vivo drug-drug interactions are predicted only with netupitant and not with its pro-drug.

Fosnetupitant has a very short half-life of 12 to 28 min in rats and dogs.

An overview of the PK parameters of fosnetupitant and netupitant after single IV administration, as well as a detailed description of the animal data on fosnetupitant, is provided in the current IB of IV NEPA FDC. [8]

1.3.1.2 Netupitant

A detailed description of the netupitant animal data is provided in the current Investigator's Brochure for the oral netupitant/palonosetron (300 mg/0.5 mg) fixed dose combination (oral NEPA FDC). [6]

1.3.1.3 Fosnetupitant in combination with Palonosetron

Safety Pharmacology

A 2-week IV cardiovascular functions study in dogs has been performed (NEPA-13-76). Alterations in atrio-ventricular conduction, ventricular depolarization and repolarization characterized by increases in PR, PQ, QT interval and QRS complex durations, ST segment as well as in corrected QT (QTc) and QT shift were observed at the top dosed group with fosnetupitant – palonosetron at 13.2/6 mg/kg/day. These effects tended to appear after 7 days of dosing and disappeared on the 14th dosing day.

Toxicology

A 4-week IV toxicity study in rats followed by a 2-week recovery period has been performed (NEPA-13-51). Assessment of fosnetupitant toxicity in combination with palonosetron was performed in rats after daily IV administration for 4 weeks including a 2-week recovery period at the following doses: fosnetupitant/palonosetron 0, 3.95/1, 13.16/3 and 39.47/10 mg/kg/day. The mortality evaluation showed that there was 1 female in the high dose group, and 4 animals in the satellite groups (2 males in the high dose group, 1 female in the mid-dose group and 1 female in the high dose group). No

cause of death was identified for these animals. No relevant changes were observed in ophthalmoscopy, hematology, coagulation and urinalyses. In high dose group, increases of alanine aminotransferase, aspartate aminotransferase and cholesterol were detected. In addition, females from the same treated group showed a decrease of urea. The above changes could be related to the liver centrilobular hypertrophy observed at histopathological examination (centrilobular hypertrophy associated with increased cytoplasmic eosinophilia, being of moderate degree in the males and of mild degree in the females). Since it was not associated with any other alteration (i.e., necrosis or inflammation), it was not considered as an adverse effect. Changes recorded during the dosing phase showed complete reversibility, with a partial recovery for aspartate aminotransferase in males. All treated animals were exposed to fosnetupitant. The pro-drug was highly distributed in the tissues and rapidly converted to netupitant which tended to accumulated after 28 days of treatment. M1 was the major metabolite present in plasma and brain and accumulate more than netupitant. All animals were exposed to palonosetron. There was a slight accumulation, however it was rapidly eliminated. The dose level of 13.16/3 mg/kg/day of fosnetupitant/palonosetron was the NOEL for systemic and local effects, and the dose level of 39.47/10 mg/kg/day the NOAEL for local and systemic effects.

A 4-week IV toxicity study in dogs followed by a 2-week recovery period has been performed (NEPA-13-52). The potential toxicity of fosnetupitant was assessed when administered once daily to dogs by IV route for 4 weeks including a 2-week recovery period. The doses were fosnetupitant/palonosetron 0, 1.316/1, 3.95/3 or 13.16/10-6 mg/kg/day (the dose level of palonosetron was decreased to 6 mg/kg/day from dosing day 15 for males and dosing day 14 for females). No mortality was observed over the course of this study. Transient clinical signs were observed (convulsive episodes, vocalization and startle movements) in 1/5 male and 2/5 females during the second week of dosing at the highest dose combination. Palonosetron in this combination was decreased from 10 to 6 mg/kg/day. Transient tremors and salivation, and indurations/swellings at the injection sites in the high dose group were also observed. Treatment-related decreased body weight gain occurred in males and females at all the three dose levels with the most severe effects in females at the highest dose level. These body weight effects were associated with a decrease in food consumption at both high and middle dose levels mainly observed during the two first weeks of the dosing phase. All these changes in body weight and food consumption were reversible after a 2-week treatment-free period and none of these changes were considered to be adverse. No treatment-related changes were recorded in ophthalmoscopy, clinical chemistry, hematology, coagulation, and urinalysis evaluations. ECG evaluations disclosed transient and reversible increased heart rate at mid dose (females only) and at high dose (both sexes) levels. These changes were associated with a transient and reversible increase (without dose-related effect) in QTc (QTcF and QTcV) intervals at the high dose level (male and female animals) and at the mid dose (males only). No treatment-related changes were noted in organ weights and no macroscopic findings were noted at the terminal or recovery sacrifice. Changes were noted at the injection sites of the females treated at the highest dose combination. Specifically, in some injected sites, subchronic inflammation of the blood vessels, as well as subchronic inflammation and necrosis at the

perivascular area, were noted. All treated animals were exposed to the combination fosnetupitant and palonosetron, in a quite proportional manner. Data indicated a quite rapid conversion of the fosnetupitant to netupitant. M1 was the main metabolite present in plasma, with an exposure which exceeded that of netupitant on Day 28. Accumulation was also observed in heart tissues for M1. No measurable levels of fosnetupitant and metabolite M2 were detected in heart samples of all treatment groups analyzed at termination. Mean heart concentration of netupitant in low dose animals was approximately 5-fold higher, when compared to plasma C_{max} on Day 28. After 14 days treatment-free period, heart level of netupitant was reduced by 83% for males and 66% for females compared to Day 30. In addition, the presence of M1 was decreased almost completely in male animals. After a repeated administration of palonosetron in combination with fosnetupitant, no significant sex differences in exposure were noted. The NOEL was 1.316/1 mg/kg/day for fosnetupitant/palonosetron.

1.3.1.4 Summary

Overall, the non-clinical safety profile of the IV NEPA FDC is comparable to that of the registered oral NEPA FDC (Akynzeo®).

1.3.2 Summary of Phase 1 Clinical Data (Human Pharmacokinetics) of Fosnetupitant and Netupitant

1.3.2.1 Absorption

Fosnetupitant IV administration

Fosnetupitant is rapidly converted to netupitant in vivo following IV administration in humans. The biotransformation of fosnetupitant to netupitant in vivo is almost completed (more than 99%) within 30-60 min after the end of the fosnetupitant infusion (study PNET-12-23 [9]). Residual fosnetupitant plasma concentrations lower than 5 ng/mL were still observed in plasma up to 3 to 6 hours after administration of the highest doses of 325 and 390 mg fosnetupitant. Concentrations of netupitant released from its pro-drug raised progressively in plasma after IV fosnetupitant administration reaching peak plasma concentrations 0.5 – 0.8 hours after the end of the fosnetupitant infusion. [8]

The recently completed PK study in cancer patients (NEPA-15-19, [10]) showed that maximum concentrations of fosnetupitant were achieved at the end of the 30-min IV NEPA FDC infusion. Unchanged fosnetupitant disappeared rapidly from the systemic circulation. Half-an-hour after the end of the infusion, the mean plasma concentration of fosnetupitant was less than 1% of the mean end-of-infusion concentration. Netupitant maximum concentrations were achieved in most of the patients at the end of the fosnetupitant infusion (median t_{max} 0.56 h), indicating fast formation of netupitant from its pro-drug.

Netupitant exposure in patients after 260 mg IV fosnetupitant administration as IV NEPA FDC was similar to that reported in healthy volunteers after a single 260 mg IV fosnetupitant infusion (study PNET-12-23) [9]).

Netupitant oral administration

In single dose oral studies conducted with the administration to healthy volunteers, measurable plasma netupitant concentrations were detected between 45 minutes and 3 hours after dosing. Plasma concentrations followed a first order absorption process and reached C_{max} in approximately 5 hours. [6]

1.3.2.2 Distribution

The mean 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. [6]

1.3.2.3 Metabolism

Netupitant is primarily excreted via hepatic/biliary routes, with renal clearance (CLr) 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 were not affected by co-administration of the CYP3A4 substrates erythromycin (500 mg) or midazolam (7.5mg). 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. [8]

A possible interaction between dexamethasone (when given in a conventional dosing regimen) and netupitant was investigated in humans. An increase in the mean plasma concentrations of dexamethasone in the presence of orally administered netupitant was shown. This increase suggests that dexamethasone doses need to be reduced when given with netupitant. [8, 11]

For interaction between dexamethasone and IV administered fosnetupitant, reference is made to Section 1.3.3 Clinical Data (PNET-13-63 [12]).

Four metabolites have been identified in human plasma at netupitant doses ≥ 30mg; metabolites M1, M2, and M3 are considered major metabolites. In a human radio-labeled 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 hours and was about 17-32 hours 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.

1.3.2.4 Elimination

The mean apparent terminal half-life of fosnetupitant ranges from 0.4 (at 65 mg fosnetupitant) to 1.2 hours (at 390 mg fosnetupitant).

The apparent mean elimination half-life of netupitant generally ranged from 30 to approximately 100 hours (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. [8]

1.3.3 Clinical Data

1.3.3.1 Fosnetupitant

Fosnetupitant has been tested in human volunteers in two studies. The first study (PNET-12-23 [9]) assessed the safety of IV fosnetupitant and determined the dose of IV fosnetupitant yielding equivalent exposure (in terms of netupitant AUC) as 300 mg oral netupitant from the oral NEPA FDC. PK data of fosnetupitant, netupitant and its metabolites M1, M2 and M3 in humans as well as safety data following IV fosnetupitant infusion at increasing doses and infusion rates were obtained. The second study (PNET-13-63 [12]) evaluated the potential drug-drug interaction between netupitant from the infused pro-drug fosnetupitant and oral dexamethasone. This study was performed to determine the dosing of dexamethasone when co-administered with the IV NEPA FDC.

Two studies have been performed in humans with fosnetupitant and, because fosnetupitant is rapidly converted to netupitant, an overview of netupitant clinical safety is additionally provided with the data of the two studies hereafter.

1.3.3.2 Netupitant Alone or in Combination with Palonosetron

The oral formulation of netupitant, as single agent or in combination with other compounds including palonosetron, has been investigated in 27 studies; 20 of them were conducted in healthy volunteers. A total of 1,939 subjects received netupitant in combination with palonosetron and 206 subjects received oral netupitant alone. [6]

Oral netupitant was generally well tolerated at all dose levels tested. In healthy volunteers, the most frequently reported treatment-emergent AEs (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. [6]

In the Phase 2 and Phase 3 studies leading to oral 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 in the current IB of oral NEPA FDC [6].

A recently completed phase 3, active-controlled, double-blind, randomized, multi-cycle safety study assessed IV NEPA FDC versus oral NEPA FDC in more than 400 cancer patients receiving HEC who were chemotherapy-naïve at study entry (NEPA-15-18, [13]). Study patients were allowed to receive the study drug in up to 4 consecutive repeated chemotherapy cycles. Study results confirmed the good safety profile and the satisfactory antiemetic efficacy of IV NEPA FDC in cancer patients receiving HEC.

An additional 36 chemotherapy-naïve or non-naïve cancer patients undergoing HEC were treated with IV NEPA FDC in an open label, single cycle, PK study (NEPA-15-19, [10]). The study confirmed the good safety profile of IV NEPA FDC.

1.4 Conclusions

Based on clinical and nonclinical data, the safety profile of the IV NEPA FDC product in humans was shown to be similar to that of oral NEPA FDC.

1.5 Study Rationale

5-HT_3 and NK_1 receptor antagonists are among the drugs of choice for an optimal antiemetic prophylaxis in cancer patients undergoing emetogenic cancer chemotherapy. The concomitant use of these agents is currently recommended for patients receiving chemotherapy of high emetic risk, and recent NCCN version 2. 2017 guidelines classify the combination of an anthracycline and cyclophosphamide in patients with breast cancer as highly emetogenic [7].

As mentioned, Helsinn recently completed a development program where the safety and tolerability of IV NEPA FDC was demonstrated in a phase 3 study in cancer patients receiving HEC in repeated chemotherapy cycles (NEPA-15-18). Despite various HEC regimens being allowed in this study, the majority of patients received cisplatin based chemotherapy.

Given that according to NCCN guidelines, prevention of AC chemotherapy-induced nausea and vomiting also calls for treatment with 5-HT_3 + NK_1 receptor antagonist prior to chemotherapy administration, NEPA-17-05 study is now performed with the aim to assess the safety and describe the efficacy of IV NEPA FDC formulation in the AC chemotherapy setting.

The dose of fosnetupitant and palonosetron to be used in the present study is the same as administered in the pivotal phase 3, double-blind, active-controlled, randomized, repeated cycle safety study NEPA-15-18 in cancer patients receiving HEC, as well as in the open label PK study in HEC cancer patients NEPA-15-19.

The present study will evaluate the safety and describe the efficacy of IV NEPA FDC (fosnetupitant/palonosetron, 260 mg/0.25 mg), given as a 30-minute infusion, in

comparison with oral NEPA FDC (netupitant/palonosetron, 300 mg/0.5 mg), given as one capsule. Target population is female breast cancer patients, who are naïve to moderately or highly emetogenic antineoplastic agents and are scheduled to receive at least 4 cycles of an AC chemotherapy regimen starting on Day 1. In addition to the oral or IV combination, study patients will also receive a regimen of oral dexamethasone as part of the anti-emetic treatment on study Day 1 of each cycle. Similar to the design of NEPA-15-18, patients will be allowed to receive the study drug in up to 4 consecutive AC chemotherapy cycles.

This study also includes exploratory assessment of the impact of dosing IV NEPA FDC and oral NEPA FDC products on resource utilization and economics.

2 STUDY OBJECTIVES

2.1 Primary

To evaluate the safety and tolerability of a single IV dose of fosnetupitant/palonosetron (260 mg/0.25 mg) combination administered as a 30-minute IV infusion with oral dexamethasone on Day 1 for the prevention of AC chemotherapy-induced nausea and vomiting in initial and repeated cycles.

2.2 Secondary

To describe the efficacy of a single IV dose of fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) administered as a 30-minute IV infusion versus a single oral dose of netupitant/palonosetron (300 mg/0.5 mg) combination (oral NEPA FDC) administered as one capsule, during the acute (0-24 hours), delayed (>24-120 hours) and overall (0-120 hours) phases of initial and repeated cycles of AC chemotherapy.

2.3 Exploratory

To evaluate the impact on economics and resource utilization through collection of Health Economics Outcomes Research (HEOR) parameters in initial and repeated cycles of AC chemotherapy.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

Time-related efficacy study parameters assessment will start at "time 0" defined as the start time of the AC chemotherapy administration on Day 1 of each cycle.

Efficacy parameters will be evaluated at each cycle in the acute, delayed and overall phases (time intervals 0 to 24 hours, >24 to 120 hours and 0 to 120 hours after the start of the AC chemotherapy administration, respectively), if not otherwise noted.

The efficacy endpoints are defined as follows:

- The proportion of patients with CR (defined as no emetic episodes and no rescue medication) during the acute, delayed and overall phases;
- the proportion of patients with no emetic episodes during the acute, delayed and overall phases;
- the proportion of patients with no rescue medication during the acute, delayed and overall phases;
- the proportion of patients with no nausea (defined as maximum nausea intensity on a 100-mm visual analog scale (VAS) < 5mm) during the acute, delayed and overall phases;
- the proportion of patients with no significant nausea (defined as maximum nausea intensity on a 100-mm VAS < 25mm) during the acute, delayed and overall phases;
- the severity of nausea (defined as the maximum nausea intensity on the 100-mm VAS) in the acute, delayed and overall phases;
- the proportion of patients with no impact on daily life (NIDL) activities in the overall phase of Cycle 1 and 2, only as assessed by the Functional Living Index-Emesis (FLIE) questionnaire. NIDL is defined as a score greater than 108 points, 54 points, and 6 points for total FLIE score, domain score, and single item score, respectively;
- the domain (nausea and vomiting) FLIE scores and the total FLIE score in the overall phase of Cycle 1 and 2, only.

3.2 Safety Assessments

Safety will be assessed in each Study Cycle, primarily by means of treatment-emergent AEs. See Section 8 ADVERSE EVENTS for specific definitions.

Additionally, the assessment of safety will be based on:

- Physical examination (PE)
- Vital signs
- Laboratory assessments (hematology and blood chemistry)

3.3 Health Economics Outcome Research (HEOR) Assessments

The following exploratory HEOR assessments will be obtained:

- Emergency Department (ED), Inpatient Admissions (IP) and length of stay (LOS)

- Lost work time and productivity assessed by the Work Productivity and Activity Impairment (WPAI) Questionnaire (Cycles 1 and 2 only)
- Disruptions in initiation and dosing of intended next cycle of chemotherapy

Additional data collected from patient diary or electronic Case Report Forms (eCRFs) may also be used for HEOR-related analysis. All parameters of interest, endpoints and analysis methods will be specified in a separate Health Economics Analysis Plan.

4 STUDY PLAN

4.1 Study Design

Multicenter, randomized, double-blind, double-dummy, parallel group, stratified study assessing the safety and describing the efficacy of a single dose of IV fosnetupitant/palonosetron (260 mg/0.25 mg) infusion versus oral netupitant/palonosetron (300 mg/0.5 mg) combination; each administered with oral dexamethasone prior to initial and repeated cycles of AC chemotherapy in female breast cancer patients.

The study is planned to be performed in approximately 50 investigational sites in the US and in approximately 30 sites distributed in Russia, Ukraine and Georgia. If necessary, additional sites and countries may be involved as well.

The present study will include female patients naïve to moderately or highly emetogenic antineoplastic agents (see section below). Adult female patients satisfying this naivety criterion, diagnosed with breast cancer and requiring treatment with an AC based chemotherapy regimen on Day 1, will be considered for enrollment in this study.

Eligible patients, stratified by region (US, non-US) and age class (age < 55 years, age ≥ 55 years), will be randomly allocated in a 1:1 fashion to receive one of the two treatment regimens (IV fosnetupitant/palonosetron 260 mg/0.25 mg administered as a 30-minute IV infusion [test] or oral netupitant/palonosetron 300 mg/0.5 mg combination) [control], before the start of AC chemotherapy on study Day 1 of Cycle 1. In subsequent cycles, patients will continue with the same study treatment they received in Cycle 1, while the dosage and components of the AC regimens administered in the repeated cycles may be different compared to Cycle 1, provided the regimen remains classified as AC.

4.1.1 Definition of naïve / non-naïve patients to moderately or highly emetogenic antineoplastic agent

Protocol Appendix 1 provides a list of oral and IV antineoplastic agents divided into 4 groups considering their emetogenic potential based on NCCN Clinical Practice Guidelines in Oncology [7].

A patient is considered "**naïve to moderately or highly emetogenic antineoplastic agents"** based on protocol Appendix 1 if she was **never previously treated** with any of the antineoplastic agents listed in Appendix 1 that fall within the high or moderate emetogenic levels for IV medications or that fall in the moderate to high emetogenic levels for oral medications. Previous antineoplastic treatment categorized as low or minimal emetogenic levels will be permitted.

4.2 Study Duration

Each randomized patient is planned to participate in a maximum of 4 consecutive AC chemotherapy cycles assessed in this study.

For each cycle, the study will include a screening visit (Visit 1) up to 7 days (up to 14 days for Cycle 1 only) before study drug administration (Day 1, Visit 2). After receiving

a single dose of active treatment on Day 1, patients will enter an efficacy evaluation period of 120 hours and then return to the clinical site on Day 6 (+2) for Visit 3. Patients will undergo a follow-up visit or telephone call (Visit 4) either on Day 15 (+3 days) or Day 22 (±3 days), depending on the next chemotherapy cycle schedule (this Visit 4 will be considered as the end of each "Study Cycle"). Visit 4, or the corresponding telephone contact, either on Day 15 (+3 days) or on Day 22 (±3 days) is to be performed prior to administering the chemotherapy relevant to the next cycle and prior to any further moderately or highly emetogenic chemotherapeutic treatment administration.

Total number of visits per patient: For each cycle, there will be a maximum of 4 visits or 3 visits plus 1 telephone contact. For all cycles, the screening visit and the study drug administration visit can be performed on the same day. The screening visit of a subsequent cycle can also coincide with the follow-up visit of the previous cycle. If all these visits are merged, Visit 4 of the previous cycle as well as Visit 1 and Visit 2 of the next cycle are all three performed on the same day. Therefore, actual number of visits in repeated cycles will depend on the number of combined visits.

Total number of cycles per patient: Each patient may participate in a maximum of 4 consecutive chemotherapy cycles, as long as they continue to fulfill the inclusion and exclusion criteria for the repeated cycles and as long as the study remains open (see below for details).

Maximum total study duration per patient is approximately 14 weeks. This maximum total study duration per patient is based on the assumption that the patient participates in 4 consecutive study cycles with 21 days interval between the Day 1 of two consecutive cycles, and that follow-up visits of one cycle coincide with screening visits of the subsequent cycle. A minimum of 14 days and maximum of 35 days is allowed between the Day 1 of two consecutive cycles.

A total of 400 patients will be randomized. Study drug assignment for Cycles 2 to 4 will be closed 7 days after the last (400^{th}) patient is randomized, in order to permit patients already screened for a subsequent study cycle to be administered study drug. Patients still participating in the study at this time should complete their current cycle and will not be allowed to enter in a subsequent cycle.

A patient will be defined as having completed a Study Cycle if she completes the follow-up visit (Visit 4) of that cycle.

A patient will be defined as "completed" if she completes Visit 4 (either as on-site visit or telephone contact) of Cycle 4. A patient will be defined as "completed cycle, not continuing" if she completes Visit 4 (either as on-site visit or telephone contact) of any cycle before Cycle 4 without continuing in the subsequent cycle. Study termination at a different time point other than Visit 4 of any cycle (including screening visit for one of the repeated cycles) will be considered as premature study discontinuation.

The overall study completion date is defined as the date of last patient's last visit or telephone contact.

4.3 Study Population

4.3.1 Number of Subjects

A total of 400 patients will be randomized, equally distributed in the two treatment groups (i.e., 200 patients/group). For further details on the sample size, please refer to Section 9.1 Sample Size Determination.

4.3.2 Inclusion Criteria

Cycle 1:

The following inclusion criteria must be checked prior to inclusion at Cycle 1:

1. Patient read, understood and signed the written informed consent before any study related activity, agreeing to participate in the study and to comply with study requirements.
2. Female patient ≥ 18 years of age.
3. Histologically or cytologically confirmed breast cancer, including recurrent or metastatic
4. Naïve to moderately or highly emetogenic antineoplastic agents (see Appendix 1).
5. Scheduled to receive at least 4 consecutive cycles of an AC combination regimen.

   Notes:
   a) additional not emetogenic, minimally or low emetogenic antineoplastic agents (see protocol Appendix 1) are permitted at any time after start of AC combination on Day 1.

   b) additional highly or moderately emetogenic antineoplastic agents (see protocol Appendix 1) are only allowed on Day 1 after the start of AC combination, provided their administration is completed within 6 hours from the start of the AC combination administration.

6. ECOG Performance Status of 0 or 1.
7. Patient shall be: a) of non-childbearing potential or b) of childbearing potential using reliable contraceptive measures and having a negative urine pregnancy test within 24 hours prior to dose of investigational product.

   Notes:

   a) Female patients of non-childberaring potential are defined as being in post-menopausal state since at least 1 year; or having documented surgical sterilization or hysterectomy at least 3 months before study participation.

   b) Reliable contraceptive measures include implants, injectables, combined oral contraceptives, intrauterine devices, vasectomized partner or complete (long term) sexual abstinence;

8. Hematologic and metabolic status adequate for receiving a cycle of AC chemotherapy based on investigator's assessment.
9. If the patient has a known hepatic or renal impairment, she may be enrolled in the study at the discretion of the Investigator.
10. Able to read, understand, follow the study procedure and complete the patient diary.

All inclusion criteria will be checked at screening visit (Visit 1 of Cycle 1); inclusion criteria #7 will be re-checked at Day 1 (Visit 2).

Cycles 2 to 4:

The following inclusion criteria must be checked prior to inclusion at each repeated cycle:

1. Participation in the study during the next cycle of chemotherapy is considered appropriate by the Investigator and does not pose unwarranted risk to the patient.
2. Scheduled to receive an AC chemotherapy regimen or AC chemotherapy together with other chemotherapies as defined in inclusion criterion #5 for Cycle 1.
3. Patient shall be: a) of non-childbearing potential or b) of childbearing potential using reliable contraceptive measures and having a negative urine pregnancy test within 24 hours prior to dosing of investigational product.
4. Adequate hematologic and metabolic status for receiving a cycle of AC chemotherapy according to the Investigator's opinion.

All inclusion criteria will be checked at screening visit (Visit 1), and inclusion criterion #3 will be re-checked at Day 1 (Visit 2) for each repeated cycle.

4.3.3 Exclusion Criteria

Cycle 1:

The following exclusion criteria must be checked prior to inclusion at Cycle 1:

1. Lactating patient.
2. Current use of illicit drugs or current evidence of alcohol abuse.
3. Scheduled to receive moderately or highly emetogenic antineoplastic agent (see protocol Appendix 1) in addition to the AC regimen, from 6 hours after the start of the AC chemotherapy on Day 1 and up to Day 1 of Cycle 2.
4. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of AC chemotherapy administration on Day 1 or between Days 1 to 5, inclusive.
5. Any vomiting, retching, or nausea (grade ≥ 1 as defined by National Cancer Institute) within 24 hours prior to the start of AC chemotherapy administration on Day 1.
6. Symptomatic primary or metastatic central nervous system (CNS) malignancy.

7. Active peptic ulcer disease, gastrointestinal obstruction, increased intracranial pressure, hypercalcemia, an active infection or any illness or medical conditions (other than malignancy) that, in the opinion of the Investigator, may confound the results of the study, represent another potential etiology for emesis and nausea (other than CINV) or pose unwarranted risks in administering the study drugs to the patient.
8. Known hypersensitivity or contraindication to 5-HT_3 receptor antagonists (e.g., palonosetron, ondansetron, granisetron, dolasetron, tropisetron, ramosetron), to dexamethasone, or to NK_1 receptor antagonists (e.g., aprepitant, rolapitant).
9. Known contraindication to the IV administration of 50 mL 5% glucose solution.
10. Participation in a previous clinical trial involving IV fosnetupitant or oral netupitant administered alone or in combination with palonosetron.
11. Any investigational drugs taken within 4 weeks prior to Day 1, and/or is scheduled to receive any investigational drug (other than those planned by the study protocol) during the present study.
12. Systemic corticosteroid therapy within 72 hours prior to the start of AC chemotherapy administration on Day 1, except the dexamethasone provided as additional study drug. However, topical and inhaled corticosteroids are permitted.
13. Scheduled to receive bone marrow transplantation and/or stem cell rescue therapy during the study participation.
14. Other than as administered as part of the study protocol, any medication with known or potential antiemetic activity within 24 hours prior to the start of AC chemotherapy administration on Day 1, including:
    - 5-HT_3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron, tropisetron, ramosetron, palonosetron)
    - NK_1 receptor antagonists (e.g., fosaprepitant, aprepitant, rolapitant or any other new drug of this class)
    - benzamides (e.g., metoclopramide, alizapride)
    - phenothiazines (e.g., prochlorperazine, promethazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine)
    - benzodiazepines (except if the subject is receiving such medication for sleep or anxiety and has been on a stable dose for at least seven days prior to Day 1).
    - butyrophenones (e.g., haloperidol, droperidol)
    - anticholinergics (e.g., scopolamine, with the exception of inhaled anticholinergics for respiratory disorders, e.g., ipratropium bromide)
    - antihistamines (e.g., cyclizine, hydroxyzine, diphenhydramine, chlorpheniramine)
    - domperidone
    - mirtazapine
    - olanzapine
    - prescribed cannabinoids (e.g., tetrahydrocannabinol or nabilone)
    - Over The Counter (OTC) antiemetics, OTC cold or OTC allergy medications.

15. Scheduled to receive any strong or moderate inhibitor of CYP3A4 (see protocol Appendix 3) during the efficacy assessment period (Day 1 to Day 5, inclusive) or its intake within 1 week prior to Day 1.
16. Scheduled to receive any CYP3A4 inducer (see protocol Appendix 3) during the efficacy assessment period (Day 1 to Day 5, inclusive) or its intake within 4 weeks prior to Day 1, with the exception of corticosteroids (for which exclusion criterion #12 applies).
17. History or predisposition to cardiac conduction abnormalities, except for incomplete right bundle branch block.
18. History of risk factors for Torsades de Pointes (heart failure, hypokalemia, family history of Long QT Syndrome).
19. Severe or uncontrolled cardiovascular diseases, including myocardial infarction within 3 months prior to Day 1, unstable angina pectoris, significant valvular or pericardial disease, history of ventricular tachycardia, symptomatic Congestive Heart Failure (CHF) New York Heart Association (NYHA) class III-IV, and severe uncontrolled arterial hypertension.

All exclusion criteria with the exception of criteria #5, #12, and #14 will be checked at screening visit (Visit 1). Exclusion criteria #5, #12, and #14 will be checked at Day 1 (Visit 2) only. Exclusion criteria #3, #4, #11, #13, #15, and #16 need to be re-checked at Day 1 (Visit 2).

Cycles 2 to 4:

The following exclusion criteria must be checked prior to inclusion at each repeated cycle:

1. Scheduled to receive moderately or highly emetogenic antineoplastic agent (see protocol Appendix 1) in addition to the AC regimen, from 6 hours after the start of the AC chemotherapy on Day 1 of current cycle and up to Day 1 of the next cycle.
2. Active infection or uncontrolled disease that may pose unwarranted risks in administering the study drugs to the patient.
3. Started any of the prohibited medications (see protocol Section 5.14).
4. Any vomiting, retching, or nausea (grade $\geq$ 1 as defined by National Cancer Institute) within 24 hours prior to the start of AC chemotherapy administration on Day 1.
5. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of AC chemotherapy administration on Day 1 or between Days 1 to 5.
6. Symptomatic primary or metastatic CNS malignancy.
7. Any illness or medical condition that, in the opinion of the investigator, may confound the results of the study or pose unwarranted risks in administering the investigational product or dexamethasone to the patient.

All exclusion criteria, with exception of criterion #4, will be checked at screening visit (Visit 1). Exclusion criterion #4 will be checked at Day 1 (Visit 2) only. Exclusion criteria #2, #3 and #5 need to be re-checked at Day 1 (Visit 2).

5 STUDY DRUG MANAGEMENT

5.1 Description of Investigational Medicinal Product

Test drug

Name:	**IV fosnetupitant/palonosetron combination (IV NEPA FDC)**
Dosage form:	Glass vial with lyophilized powder (for IV infusion)
Strength:	260 mg fosnetupitant*/0.25 mg palonosetron per vial
Reconstitution:	50 mL sterile 5% glucose solution per vial
Reconstituted fosnetupitant/palonosetron solution;	50 mL solution of 5.2 mg/mL fosnetupitant and 5 µg/mL palonosetron
Dosing	IV infusion of 30 minutes duration beginning 30 minutes prior to the start of AC chemotherapy administration
Route of administration:	IV infusion

**260 mg fosnetupitant (chloride hydrochloride), corresponding to 235 mg fosnetupitant*

Control drug

Name:	**Oral netupitant/palonosetron combination (oral Akynzeo ®)**
Dosage form:	Blistered Hard gelatin capsule
Strength:	300 mg netupitant/0.50 mg palonosetron
Dosing:	To be administered 60 minutes prior to the start of AC chemotherapy administration
Route of administration:	Oral

Placebo for Test drug

Name:	Placebo for IV NEPA FDC
Dosage form:	Glass vial with lyophilized powder (for IV infusion)
Strength:	NA (not applicable)
Reconstitution:	50 mL sterile 5% glucose solution per vial
Reconstituted placebo solution;	50 mL placebo solution
Dosing	IV infusion of 30 minutes duration beginning 30 minutes prior to the start of AC chemotherapy administration
Route of administration:	IV infusion

Placebo for Control drug

Name:	Placebo for oral Akynzeo®
Dosage form:	Blistered Hard gelatin capsule
Strength:	NA (not applicable)
Dosing:	To be administered 60 minutes prior to the start of AC chemotherapy administration
Route of administration:	Oral

5.2 Additional Non-investigational Study Drug

Additional non-investigational study drug (administered to both treatment groups)

Name:	Dexamethasone
Dosage form:	Blistered tablets
Strength:	4 mg
Dosing:	Day 1: 3 tablets of 4 mg, 12 mg in total, once (30 minutes prior to the start of the AC chemotherapy administration [immediately before the start of the IV NEPA FDC or placebo infusion].
Route of administration:	Oral

5.3 Treatment Groups

Patients eligible for the study will be randomly assigned (1:1 ratio, stratified by region and age class) to one of the two treatment groups:

Group 1 / Test group – IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) administered as a 30-minute infusion of a 50 mL solution on Day 1 of each cycle.

Group 2 / Control group – oral netupitant/palonosetron (300 mg/0.50 mg) (oral NEPA FDC) on Day 1 of each cycle.

Oral dexamethasone (12 mg) will be administered on Day 1 of each cycle to both test and control groups.

5.4 Dose and Administration

Test drug: The 30-minute (+/-5 minutes) IV NEPA FDC infusion will start 30 minutes prior to the start of AC chemotherapy administration at each cycle. The IV infusion will be completed before starting chemotherapy administration.

To minimize the loss of investigational medicinal product (IMP) remaining in the infusion line after the end of IMP infusion, the following process is to be followed:

1. At the end of the 30 +/-5 min IMP or placebo infusion, the infusion line drip chamber is to be empty.
2. The Investigator or designated responsible person will ensure completeness of IV infusion administration by rinsing the infusion line with 20 to 30 ml sterile 5% glucose solution or sterile 0.9% saline solution. Calcium or magnesium containing solutions (e.g., Lactated Ringer solution, etc) are not allowed. The infusion line rinsing process is to be performed immediately after the end of IMP or placebo infusion and is to be completed before to start the AC chemotherapy administration.

Control drug: Oral NEPA FDC (Akynzeo®) capsule will be administered 60 minutes prior to the start of AC chemotherapy administration at each cycle.

For blinding purposes, the double-dummy technique will be applied. Patients will be administered with placebos for test and control drugs, as applicable (see Section 5.10 Blinding).

Additional non-investigational study drug (administered to both treatment groups):

Oral dexamethasone administration will be performed in open fashion since dose and schedule are identical between test and control treatments.

On Day 1 of each cycle, oral dexamethasone (3 tablets of 4 mg, for a total dose of 12 mg) will be taken 30 minutes prior to the start of the AC chemotherapy administration (immediately before the start of the IV NEPA FDC or placebo infusion).

5.5 Packaging and Shipment

The IMPs will be provided in a sealed, blinded and appropriately labeled study kit. Each study kit is patient-specific and will provide the necessary supply for one study cycle.

Each study treatment kit will contain:

- 1 capsule of oral treatment (oral NEPA FDC capsule or matching placebo capsule)
- 1 vial for IV treatment (IV NEPA FDC or matching placebo vial) with lyophilized powder
- 3 blistered dexamethasone 4 mg tablets
- 1 container with 50 ml 5% glucose solution for infusion
- 1 single use plastic device for reconstitution process (Ecoflac® Connect)

The infusion line and the infusion line rinsing solution (either 5% glucose or 0.9% saline solution) will not be provided in the study kit.

Sealed treatment kits, all identical in appearance and identified by a kit number, will be supplied in a blinded fashion. The first kit will be assigned to the patient at the time of randomization, after confirmation of eligibility criteria, by the Interactive Web Response System (IWRS). At each subsequent cycle, the IWRS will automatically allocate to the patient a kit of the same treatment group.

Study kits may be either manufactured with single panel label in English only for exclusive use in US, or with multilanguage booklet labels intended for use in any of the study countries.

The study drugs and their placebos will be identical in color, smell, size and appearance thereby enabling a double-blind design.

The treatment kit's outer box and all components contained will carry a label with the information in accordance with applicable rules.

Study kit packaging will be performed by Catalent Germany Schorndorf GmbH. Local depots under control of Catalent will be considered for storage and distribution of the study kits to the sites in US, Russia, and Ukraine, while drug will be directly delivered from Catalent Schorndorf to Georgian sites.

The study kits, together with relevant documentation, will be supplied from the depots to a designated pharmacist at the hospital site or directly to the Investigator or designee, as applicable.

Relevant labels will carry a removable portion (peel-off) to be applied on study records in order to certify the correct distribution, preparation and administration of the study drugs.

The hospital pharmacist or a designated responsible person from the site staff will be requested at each cycle to select the IWRS-determined study kit, prepare and provide the study drugs and other materials to the Investigator or designee. At the time of preparing the study drug for dispensing to the Investigator or designee, the pharmacist or designated responsible person will fill in the blank space on the relevant label with the patient number appearing on the IWRS randomization confirmation.

All the necessary detailed information relative to the characteristics of the study drugs, their receipt, storage, preparation, administration and return is reported on the Study Drug Manual that will be provided to the sites prior to the start of the study.

5.6 Storage

The study drug will be delivered and stored between 2 and 8°C (between 35.6 and 46.4°F), 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 study 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.

5.7 Drug Depots

The study kits are shipped from the Catalent central depot of Schorndorf (Germany) to local depots and, from there to the study sites. The study kits will be stored at the local depots until shipments to the investigational sites are triggered via IWRS.

5.8 Accountability

Once the study kits are received at the study site, the pharmacist or designated responsible person will sign the drug receipt form and notify via IWRS the clinical supplies receipt. Adequate records of the receipt, dispensation and return of study kits must be maintained throughout the study. Used study kits will be retained until the drug accountability forms have been checked by a designated monitor. Unused study kits remaining at investigational sites at the end of the study will be destroyed by returning to the drug depots or using a local vendor for disposal. At the end of the study, delivery records will be reconciled with those of used and returned stocks. Any discrepancy will be accounted for. Destruction of unused medication will be documented in writing according to FDA Investigational New Drug (IND) regulation 21CFR312.59, ICH Good Clinical Practice (GCP) and the drug depot Standard Operating Procedures (SOPs). Any destruction of remaining study medication material by the study sites is to be first approved in writing by the study Sponsor.

5.9 Administration of Study Treatment

At Day 1 (Visit 2) of Cycle 1, after confirming patient's eligibility, the Investigator or designee will get connected to the IWRS to randomize the patient. The IWRS will assign a kit number to the patient and the Investigator (or Investigator's designee) will receive the IWRS notification mentioning the kit number assigned to the patient for which the request was made. The hospital pharmacist, or designated responsible person, will select from the study kits stored at the site pharmacy the corresponding kit as indicated by the IWRS and fill-in the blank space(s) on the outer study kit label with the patient's identification number which was assigned by IWRS during screening.

In the case the pharmacist or designated responsible person is only involved in the site storage of the study kits but not in the preparation of the investigational products, the pharmacist or designated responsible person will:

- select the study kit
- fill in the outer study kit box label with the patient identification number
- document the selection and distribution of the entire and still sealed kit to the Investigator or Investigator's designee for preparation by attaching the outer study kit box label peel-off onto the Study Drug Inventory log.

In the case the pharmacist or designated responsible is involved in both the site storage of the study kits and in the preparation of the investigational products, the pharmacist or designated responsible person will:

- select the study kit
- fill in the outer study kit box label and the peel-off portions from the other study kit components with the patient identification number
- document the selected kit by attaching the filled in outer study kit box label peel-off onto the Study Drug Inventory Log
- open the kit and prepare the investigational products as detailed in the Study Drug Manual documenting the preparation by completing and attaching the study drug (or placebo) vial peel-off label onto the Study Drug Preparation & Administration Log
- provide the ready to use study medication to the Investigator or designated person.

The IV infusion prepared by the pharmacist or designated person (or Investigator's designee) is to be kept at room temperature, protected from direct sunlight and is to be administered within 3 hours from end of preparation (reconstitution process). The end time of preparation and the end time of infusion are to be considered with respect to this requirement.

Once the IV study drug (or placebo) and the wallet with oral study drug (oral Akynzeo® or placebo capsule) and dexamethasone tablets are ready, they will be provided to the Investigator or designee for patient's administration.

At each subsequent cycle (Cycles 2 to 4), the Investigator or designee will get connected to the IWRS to obtain a kit number for the repeated cycle and the same above described procedure will apply.

Adequate written instructions (in form of a Study Drug Manual) for use for the pharmacist or designated person will be provided to him/her for the preparation of the study medication at each study site.

The relevant labels on the study drug will be filled in according to the provided instructions.

Administration process and relevant times:

One (1) capsule of blinded study drug (either of netupitant/palonosetron combination or matching placebo) is to be taken with a glass of non carbonated water 60 minutes prior to the scheduled start of AC chemotherapy administration on Day 1.

Thirty minutes prior to the scheduled AC chemotherapy administration start, the 3 dexamethasone tablets (each containing 4 mg dexamethasone) are also to be taken by the patients with a glass of non carbonated water.

Immediately after the administration of the oral dexamethasone on Day 1, the 30-minute (+/- 5 minutes) blinded IV infusion (either of fosnetupitant/palonosetron combination or matching placebo) solution will be started.

The IV NEPA FDC or placebo vial content, previously reconstituted with 50 mL glucose 5% solution for IV infusion, will be started as a 30-minute (+/- 5 minutes) infusion.

At the end of the IV NEPA FDC or placebo infusion, the Investigator or designated person will ensure that the infusion line drip chamber is empty. The Investigator or responsible person will then immediately proceed with rinsing the infusion line with 20 to 30 ml of sterile 5% glucose solution (or sterile 0.9% saline solution), to ensure complete administration of the IV NEPA FDC or placebo infusion. Calcium or magnesium containing solutions (i.e., Lactated Ringer solution, etc) are not allowed. The infusion line rinsing process is to be completed before to start the AC administration.

The infusion of the scheduled AC chemotherapy will then be started immediately after the infusion line rinsing process is completed, and the starting time of AC will be considered as “time 0” for the antiemetic efficacy assessments (see Section 7.1 Efficacy Assessments).

The administration of the AC components is to be performed according to local standard practice.

Treatment administration schedules in chronological order and inclusive of the allowed time windows are provided below, including the infusion line rinsing process. For all time windows, reference is made to the start of AC chemotherapy infusion.

<table>
<tr><td></td><td>Group 1 (Test)</td><td>Group 2 (Control)</td></tr>
<tr><td rowspan="6">Day 1</td><td>1 capsule NEPA FDC placebo oral, 60 minutes before start of AC chemotherapy administration</td><td>1 capsule Akynzeo® (300 mg netupitant/0.50 mg palonosetron), oral., 60 minutes before start of AC chemotherapy administration</td></tr>
<tr><td colspan="2">Time window for capsule administration: the capsule administration is to be performed between 75 and 55 min before start of AC</td></tr>
<tr><td colspan="2">3 tablets, 4 mg dexamethasone 30 minutes before start of AC chemotherapy (immediately before the start of the IV NEPA FDC infusion)
Time window: 45 to 30 min before start of AC</td></tr>
<tr><td>IMP infusion:
1 vial, 260 mg fosnetupitant/ 0.25 mg palonosetron reconstituted with 50 mL 5% glucose solution and administered by IV as a 30-minute (+/- 5 minutes) infusion, starting 30 minutes before AC chemotherapy administration</td><td>IMP placebo infusion:
1 vial, fosnetupitant/palonosetron placebo reconstituted with 50 mL 5% glucose solution and administered by IV as a 30-minute (+/- 5 minutes) infusion, starting 30 minutes before AC chemotherapy administration</td></tr>
<tr><td colspan="2">Time window for infusion administration: the 30min +/-5 min infusion of IMP is to be started between 45 and 30 minutes before the start of AC administration.</td></tr>
<tr><td colspan="2">Infusion line rinsing process:
The infusion line rinsing with 20 to 30 ml solution (see above) is to be started immediately after the end of IMP or placebo infusion and is to be completed before the start of AC administration.</td></tr>
</table>

5.10 Blinding

The blinding of the study drugs is guaranteed by the use of identical placebos to the respective active drugs (double-dummy technique).

5.10.1 Emergency Unblinding Procedure

The Investigator has the possibility to unblind the study treatment in case of an emergency situation, when he/she considers essential to know what treatments the patient has received. Any unblinding of the study treatment will be performed by IWRS (24-hour 7-day coverage). If the code is broken by the Investigator, the patient should be discontinued from the study. The date and reason for unblinding are included in eCRF. The IWRS will promptly notify, in a blinded fashion, the Sponsor and the CRO Clinical Monitor when a treatment code has been unblinded by the Investigator.

The unblinding procedure is described in detail in a specific document (IWRS User Manual) that will be provided separately to the Investigator.

5.11 Randomization - Use of IWRS

Randomization will be used to avoid bias in assigning treatments to patients. Randomization tends to produce treatment groups in which the distributions of prognostic

factors, known and unknown, are similar; it also enhances the validity and the efficiency of statistical comparisons between the treatment groups.

Treatment assignment will be managed through a static central blocked randomization stratified by region (US, non-US) and age class (age < 55 years, age ≥ 55 years). Randomization scheme will be reproducible and will be prepared prior to start of the study via a computerized system by the IWRS vendor. A master randomization list copy will be filed securely by this vendor and the Sponsor in a manner that ensures that blindness is properly maintained throughout the trial. The biostatistician involved in the creation of randomization lists will not take part in any study activities.

Considering the strata, eligible patients will be assigned to one of the two arms, in a balanced ratio (1:1), according to specific procedures using the IWRS.

Separate lists (packaging list and patient's randomization list) will be prepared for patients' randomization and study medication packaging. Sealed cartons (kits) containing the study medications will be prepared according to the 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.

At Day 1 (Visit 2) of Cycle 1, after confirmation of patient eligibility, the Investigator will get connected to the IWRS for randomization and communicate to the system the unique patient identification number (assigned by IWRS at the screening visit) and the patient's date of birth.

The system will then assign to the patient the treatment that corresponds to the first free treatment available in the relevant list and the IWRS will randomly select a kit number among the kits available at the site and containing the selected treatment. The IWRS notification form will be sent by e-mail to the Investigator, describing the kit number to be dispensed to the patient. The unique patient identification number, the kit number assigned to the patient, the patient randomization number as well as the other patient characteristics, are stored in the system. In particular, the patient randomization number is stored in the system but is not communicated to the Investigator. The randomization procedure only proceeds if kits of both treatments are available at site.

The hospital pharmacist or designated responsible person will select the appropriate carton of study medication based on the kit number supplied by the IWRS.

Relevant carton box peel-off label from the selected study kit will be attached to the Study Drug Inventory Log by the pharmacist or designated person to document the correct kit's assignment. The peel-off labels from the other study kit component will then be applied on the Study Drug Preparation & Administration log by the Investigator as a proof that the correct medication has been prepared and administered to the patient.

On Day 1 of each repeated cycle (i.e., Cycles 2 to 4), the Investigator will get connected to the IWRS to access the kit number to be assigned to the patient (i.e., a kit containing the same treatment as assigned in the first cycle will be automatically selected). An IWRS form will be sent by the system to the Investigator, communicating the selected kit number for the repeated cycle.

Due to the blinded study design, neither the Sponsor, nor the pharmacist, the Investigator, the patient or the Contract Research Organization (CRO) will know which treatment is administered. The monitor who will check the drug accountability forms (the Study Drug Inventory Log with the peel-off from the carton box attached by the pharmacist and the Study Drug Preparation & Administration log with the peel-offs attached by the Investigator) will also be blinded with regard to the treatment administered.

The Investigator has the possibility to unblind the study treatment in case of an emergency situation, when he/she considers essential to know what treatments the patient has received. For details, see Section 5.10.1 Emergency Unblinding Procedure. The IWRS will promptly notify, in a blinded fashion, the Sponsor and the CRO Clinical Monitor when a treatment code has been unblinded by the Investigator.

5.12 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/palonosetron to date. No antidote for palonosetron or netupitant overdose is known.

5.13 Occupational Safety

No studies have been performed on the ability to drive vehicles and operate machinery while receiving agents being evaluated in this study. If patients experience somnolence or tiredness, they should avoid potentially hazardous tasks such as driving or operating machinery.

5.14 Prior and Concomitant Medications

Information on prior and concomitant medications will be collected beginning 14 days prior to Day 1 of the first cycle up to Visit 4 (Day 15+3 days or Day 22 +/-3 days follow-up visit) of the last cycle.

Inclusion / exclusion criteria are to be carefully checked with reference to prohibited medications and relevant time periods.

5.14.1 Prior and Concomitant Medications for the Prevention of Nausea and Vomiting or With Potential Anti-emetic Effect

With the exception of study medication and planned dexamethasone as per current protocol, the use of any medication for the prevention of nausea and vomiting, or to increase the expected preventive effects of the study medication, or any medication with potential anti-emetic effects within 24 hours prior to the start of AC chemotherapy administration on Day 1 of each cycle and for the following 120 hours is prohibited.

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

- 5-HT_3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron, tropisetron, ramosetron, palonosetron)
- NK_1 receptor antagonists (e.g., fosaprepitant, aprepitant, rolapitant or any other new drug of this class)

- benzamides (e.g., metoclopramide, alizapride)
- phenothiazines (e.g., prochlorperazine, promethazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine)
- benzodiazepines (except if the patient is receiving such medication for sleep or anxiety and has been on a stable dose for at least seven days prior to Day 1)
- butyrophenones (e.g., haloperidol, droperidol)
- anticholinergics (e.g., scopolamine, with the exception of inhaled anticholinergics for respiratory disorders, e.g., ipratropium bromide)
- antihistamines (e.g., cyclizine, hydroxyzine, diphenhydramine, chlorpheniramine)
- domperidone
- mirtazapine
- olanzapine
- prescribed cannabinoids (e.g., tetrahydrocannabinol or nabilone)
- Over The Counter (OTC) antiemetics, OTC cold or OTC allergy medications.

Systemic corticosteroid therapy (including but not limited to dexamethasone, hydrocortisone, methylprednisolone, or prednisolone, and except the dexamethasone provided as additional study drug) taken within 72 hours prior to the start of AC chemotherapy administration on Day 1 and until 120 hours afterwards is not permitted. Topical and inhaled corticosteroids are allowed.

Use of cannabinoids for non-medical purposes (e.g., recreational use), or other illicit drugs, is not permitted between within 24 hours prior to AC chemotherapy administration on Day 1 and until 120 hours afterwards.

In addition to study treatment, rescue medication for treatment of nausea and vomiting is permitted at any time after the start of AC chemotherapy administration in case of need (see Section 5.15 Rescue Medication).

5.14.2 Prior and Concomitant Cancer Chemotherapy and Radiotherapy

At study entry, patients must be naïve to moderately or highly emetogenic antineoplastic agents based on protocol Appendix 1. They must also be scheduled to begin the first cycle of an AC chemotherapy regimen starting on Day 1.

Other antineoplastic agents are allowed in association to AC, provided the following conditions are satisfied:

- any additional antineoplastic agent on Day 1 is to be administered after the start of the AC combination administration
- additional not emetogenic, minimally or low emetogenic antineoplastic agents are permitted at any time after start of AC combination on Day 1 of Cycle 1
- additional highly or moderately emetogenic antineoplastic agents are allowed on Day 1 only of each study cycle, provided their administration is completed within 6 hours from the start of the AC combination administration. No moderately or highly emetogenic antineoplastic agents are allowed from 6 hours after the start of the AC chemotherapy on Day 1 of each cycle and up to Day 1 of the next cycle.

Of note, in Cycles 2 to 4, the dosage and components of the AC regimens administered in the repeated cycles may be different compared to cycle 1, provided the regimen remains classified as AC.

Please refer to Appendix 1 for classification of antineoplastic agents based on their emetogenicity level.

Radiation therapy to the abdomen or the pelvis is not permitted within 1 week prior to Day 1 of each cycle, during Day 1 and during the period from Day 1 to Day 5, inclusive for each study cycle.

5.14.3 Other Prior and Concomitant Medications

All medications taken by the patient within 14 days prior to Day 1 of Cycle 1, or administered as clinically indicated, during the study and up to Visit 4 of the last study cycle, are to be recorded on the appropriate eCRF pages.

Regarding the use of CYP3A4 inducers and inhibitors (see Appendix 3 for list of examples):

- Strong or moderate CYP3A4 inhibitors: are not allowed during the efficacy assessment periods (Day 1 to Day 5, inclusive of each study cycle) and within 1 week prior to Day 1 of each cycle, in accordance with exclusion criterion #15.
- CYP3A4 inducers: in accordance with exclusion criterion #16, CYP3A4 inducers are not allowed from 4 weeks prior to Day 1 of Cycle 1 (with the exclusion of glucocorticoids as described below) until Day 5 (inclusive) of the last study cycle.

Despite classified as CYP3A4 inducers, systemic glucocorticoids are forbidden during the 72 hours before AC chemotherapy administration on Day 1, in accordance with exclusion criterion #12.

In accordance with exclusion criteria, any investigational drugs taken within 4 weeks prior to Day 1 of Cycle 1 or planned during the study are not allowed. For this purpose “Other investigational product" has to be intended as any agents tested in clinical trials, even those which are tested for indications that are already approved (e.g., comparison of one type of chemotherapy versus another one).

Prophylactic infusion of saline or other hydration solutions prior to or after chemotherapy in order to prevent toxic reactions related to chemotherapy is to be recorded on the appropriate eCRF page; this should also include rehydration events that occur outside of the clinical site.

Infusion of blood products is to be recorded.

All medications administered in relation to diagnostic procedures, e.g., anesthetics and antibiotics are to be recorded.

5.15 Rescue Medication

Rescue medication is defined as any medication administered to alleviate established, refractory or persistent nausea or vomiting after the start of chemotherapy on Day 1 and up to Day 5, inclusive, of each cycle.

Rescue medication will be permitted on an as-needed basis.

NK_1 receptor antagonists, commercial palonosetron (Aloxi®, Onicit®, Paloxi®) and commercial Akynzeo® are not allowed as rescue medications. Other 5-HT_3 receptor antagonists should not be used as rescue medications.

For additional details also refer to Section 7.1.2 Rescue Therapy.

5.16 Treatment Compliance

A patient will be considered to be compliant with therapy if she takes all study drugs (including dexamethasone) provided in the clinical study medication kit. Compliance will be defined overall and for each cycle.

6 STUDY CONDUCT

6.1 General Instructions

In this study, each patient may participate in a maximum of 4 consecutive chemotherapy cycles. A minimum of 14 days and maximum of 35 days is allowed between the Day 1 of two consecutive cycles.

Each "Study Cycle" will include Visit 1 (Screening Visit), Visit 2 (Day 1 Visit), Visit 3 (Day 6 +2 days Visit) and Visit 4 follow-up (either as a visit or telephone contact) on Day 15 (+3 days) or Day 22 (±3 days), depending on the chemotherapy cycle schedule. For all cycles, the screening visit and the study drug administration visit can be performed on the same day. The screening visit of a subsequent cycle can also coincide with the follow-up visit of the previous cycle. Therefore, Visit 4 of a previous cycle, as well as Visit 1 and Visit 2 of the next cycle, can all coincide and be performed on the same day.

The study visits and contacts, and the main activities characterizing them are detailed by visit / contact here below (please, also see the study Flow Chart):

Cycle 1

- Visit 1, screening visit up to 14 days prior to Day 1, during which patients will be assessed for eligibility;
- Visit 2, randomization visit at Day 1, during which patients fulfilling selection criteria will be randomized to one of the 2 treatment groups and will be treated; patient diary, FLIE questionnaire and the WPAI questionnaire will be dispensed;
- Visit 3, routine visit at Day 6 (+2), during which patients will be assessed for safety and patient diary and questionnaires will be retrieved;
- Visit 4, follow-up visit on Day 15 (+3 days) or on Day 22 (+/-3 days) on-site or phone contact for AEs and concomitant medications data collection; HEOR-related information on ED/hospitalization will also be collected.

Cycles 2 to 4

- Visit 1, screening visit up to 7 days prior to Day 1, during which patients will be assessed prior to receiving each repeated cycle of chemotherapy;
- Visit 2, Day 1, during which patients will be administered the same treatment assigned on Cycle 1 Day 1, patient diary, FLIE questionnaire and the WPAI questionnaire will be dispensed at Cycle 2 only; HEOR-related information on chemotherapy will also be collected;
- Visit 3, routine visit at Day 6 (+2), during which patients will be assessed for safety and patient diary retrieved; FLIE questionnaire and the WPAI questionnaire will be retrieved at Cycle 2 only;
- Visit 4, follow-up visit on Day 15 (+3 days) or on Day 22 (+/-3 days) on-site or phone contact for AEs and concomitant medications data collection. HEOR-related information information on ED/hospitalization will also be collected.

6.2 Study Procedures by Time Point

6.2.1 Cycle 1 - Visit 1 (screening, Day -14 to Day 1)

If the Investigator considers a patient to be potentially eligible for the study, written informed consent for participation in the study must be obtained before any study-related procedures. The patient will be screened within 14 days prior to randomization and study drug administration; the following procedures will be performed and data collected during this visit:

- Informed consent
- Eligibility criteria
- Demographic data (gender, race, date of birth)
- Alcohol, tobacco and illicit drug consumption
- Reproductive status
- Significant medical history, including surgery, based on Investigator assessment.
- Histologically or cytologically confirmed breast cancer, including recurrent or metastatic (current cancer history)
- ECOG Performance Status
- Urine pregnancy test for females of childbearing potential
- Prior and concomitant medications
- Complete physical examination (general appearance, head, eyes, ears, nose, throat, skin, neck, lungs, cardiovascular, breast, lymph nodes, abdomen, musculoskeletal and neurological)
- Vital signs (pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position)
- Laboratory tests, including hematology and blood chemistry
- Patient identification number assignment through IWRS
- AE assessment

Based on the relevant above mentioned assessments outcome, the Investigator will decide if the patient is eligible for the study.

6.2.2 Cycle 1 - Visit 2 (randomization, Day 1)

The following procedures will have to be completed:

- The relevant inclusion / exclusion criteria will be assessed for patient's eligibility confirmation (for details, see Section 4.3.2 Inclusion Criteria and Section 4.3.3 Exclusion Criteria);
- The patient will undergo pre-dose assessments, including predose vital signs (pulse rate, systolic and diastolic blood pressure after resting in semi-supine position for at least 5 minutes; weight and height);
- Urine pregnancy test for females of childbearing potential: in case the screening urine pregnancy test was performed less than 24 hours prior to the administration of the first (oral capsule) investigational product, the test is not to be repeated at Visit 2);

After confirmation of patient eligibility, the patient will be randomized to one of the two treatment groups using the IWRS.

The IWRS will provide the kit number to be dispensed to the patient. The study treatment administration schedule is the following (please also refer to Section 5.9 Administration of Study Treatment for relevant time windows):

- 60 minutes prior to the start of AC chemotherapy infusion, the patient will receive 1 capsule of study drug (oral Akynzeo®) or matching placebo;
- 30 minutes prior to the start of AC chemotherapy infusion, the patient will receive 3 tablets of 4 mg dexamethasone;
- immediately after the oral dexamethasone administration (30 minutes prior to the start of AC chemotherapy infusion), the patient will receive a 30-minute (+/-5 minutes) infusion of study drug (IV NEPA FDC) or matching placebo;

At the end of the IV infusion, and before to start AC administration, the infusion line used for the IMP infusion is to be rinsed with 20 to 30 ml sterile 5% glucose solution, or sterile 0.9% saline solution, to ensure complete IMP administration. See details below.

The date and the precise time (hh:mm) of the study drug (oral capsule) and additional study drug administration (dexamethasone tablets) must be recorded in the source records as well as on the relevant eCRF page.

For the IV NEPA FDC or placebo infusion, start and stop times (including any interruptions and re-start, if applicable) are to be collected.
The relevant tear-off labels from the study drug kit will be attached to the Study Drug Inventory Log (by the pharmacist or designated responsible person) and drug administration form (by the Investigator) (see Section 5.9 Administration of Study Treatment).

For the IV NEPA FDC or placebo infusion, information on the patient's arm where the infusion will be applied, or any other information regarding infusion location will also be collected in the eCRF.

Infusion Line rinsing process after the end of IV NEPA FDC or placebo infusion:

The infusion line rinsing at the end of the IMP or placebo infusion is to be performed with 20 to 30 ml of either sterile 5% glucose solution or sterile 0.9% saline solution. Calcium or magnesium containing solutions (i.e., Lactated Ringer solution, etc) are not allowed. The line rinsing is to start immediately after the end of the IV NEPA FDC or placebo infusion, following verification that the drip chamber is empty. The rinsing process is aimed at ensuring the complete IMP administration. The infusion line rinsing process is to be completed before to start the AC administration. Confirmation of the performed rinsing process and the type of solution used will be documented in the eCRF.

- One (1) hour after the administration of the oral capsule, after the end of the 30-minute (+/- 5 minutes) IV infusion and after completion of the infusion line rinsing process, the AC chemotherapy will be administered to the patient. Information on the infusion arm or any other infusion location selected for the AC chemotherapy administration will be collected in the eCRF. The starting time of AC administration on Day 1 is the "time 0" for the time related efficacy assessments; the starting time of AC administration will be collected in source records and in the eCRF.

- Before the start of the AC chemotherapy administration, the Investigator will provide the patient with the patient's diary and instruct her on how to complete it. The patient will start completing the diary from the start of AC chemotherapy infusion on Day 1 (time 0 for the time related efficacy assessments) and will maintain it through the following 5 days, i.e., until Day 6, 120 hours after the start of AC chemotherapy administration. The patient will be instructed to bring the diary back to the site at Visit 3.
- Concomitant Medications check and recording.
- AE assessment.
- The Investigator will provide the FLIE and WPAI questionnaires to the patient, instructing her on how to complete them and reminding the patient to bring the completed questionnaires to Visit 3.

6.2.3 Cycle 1 - Visit 3 (Day 6 [+2 days])

This visit is to be planned on Day 6, not earlier than 120 hours after start of AC chemotherapy on Day 1. In the case the visit day would fall during the week end, or in case Visit 3 cannot be performed on Day 6 after the end of the 120 hours period for any reason, a +2 days time window is allowed for the execution of this visit. The patient will return to the site to undergo the following study procedures/assessments:

- Concomitant medications
- AE assessment
- Complete physical examination (general appearance, head, eyes, ears, nose, throat, skin, neck, lungs, cardiovascular, breast, lymph nodes, abdomen, musculoskeletal and neurological). Any new or worsening of pathological findings noted since previous examination are to be reported on the Adverse Event eCRF form.
- Vital signs (pulse rate, systolic and diastolic blood pressure after resting in semi-supine position for at least 5 minutes)
- Laboratory tests, including hematology and blood chemistry
- Check and retrieval of the completed patient diary
- Check and retrieval of the completed FLIE
- For HEOR-related assessments:
    - Check and retrieval of the completed WPAI questionnaire

At this visit, the Investigator will schedule Visit 4 (follow-up Visit), either as on site visit or telephone contact. Visit 4, follow-up visit, is to be performed either on Day 15 +3 days or on Day 22+/-3 days, depending on the next chemotherapy cycle schedule. **The patient's follow-up visit or contact is to be performed prior to administering the chemotherapy relevant to the next cycle and prior to any further moderately or highly emetogenic chemotherapeutic treatment administration.**

If, for any reason, no further chemotherapy cycle is planned, Visit 4 follow-up should be performed on Day 22 (+3 days).

6.2.4 Cycle 1 - Visit 4 (follow-up visit, Day 15 [+3 days] or Day 22 (± 3 days])

Visit 4, follow-up visit, can be performed either as on site visit or telephone contact.

During Visit 4, the patient will be questioned about any new AEs appeared since the last visit or about any ongoing AE at last visit; concomitant medications, either new or ongoing will be verified and relevant data collected. For HEOR-related assessments, ED/IP/LOS information for events occurring since Day 1 will be documented.

The follow-up visit for Cycle 1 and the screening visit for Cycle 2 may coincide.

6.2.5 Cycles 2 to 4 - Visit 1 (screening, Day -7 to Day 1)

If the Investigator considers a patient to be suitable to continue the subsequent cycle of AC chemotherapy in the study, the patient will be re-assessed within 7 days prior to Day 1 of the subsequent (repeated) cycle: inclusion/exclusion criteria verification, complete physical examination, ECOG performance status, vital signs, and laboratory tests will be performed as for Visit 1 of Cycle 1. Females of childbearing potential will have to perform a urine pregnancy test.

The study Visit 1 may be performed from Day -7 up to study Day 1 inclusive (i.e., Visit 1 and Visit 2 may occur on the same day on study Day 1). In that case, the assessments planned at both Visit 1 and Visit 2 have to be performed only once. In addition, the follow-up visit of one cycle and the screening visit of the subsequent cycle may coincide.

6.2.6 Cycles 2 to 4 - Visit 2 (Day 1)

After patient has been re-evaluated for eligibility, the Investigator will get connected to the IWRS for the assignment of a new treatment kit number. The patient will be administered the same treatment assigned at Cycle 1 (Day 1, Visit 2). The procedures to be completed are the same as for Cycle 1 (Day 1, Visit 2), except for (a) randomization, i.e., for repeated cycles IWRS will only provide a new kit number for the patient, according to the patient's randomization at Cycle 1, and (b) the FLIE questionnaire and the WPAI questionnaire will be dispensed in Cycle 2, but not in Cycle 3 or Cycle 4. In addition, starting at Cycle 2 Visit 2 (Day 1), the Investigator will document if changes in chemotherapy administration from the previous cycle occurred and will note any delays in treatment for the current cycle.

6.2.7 Cycles 2 to 4 - Visit 3 (Day 6 [+2 days])

On Day 6 (+2), the patient will return to the site and will undergo the same study procedures/assessments as for Visit 3 of Cycle 1. However, the FLIE questionnaire and the WPAI questionnaire will not be administered during Cycle 3 and Cycle 4.

6.2.8 Cycles 2 to 4 - Visit 4 (follow-up visit, Day 15 [+3 days] or Day 22 (± 3 days])

Visit 4, the follow-up visit, can be performed either as on site visit or telephone contact, and the patient will undergo the same study procedures/assessments as for Visit 4 of Cycle 1.

The follow-up visit of one cycle and the screening visit of the subsequent cycle may coincide.

6.3 Definition of Study Completion

A patient will be defined as having completed a Study Cycle if she completes the follow-up visit (Visit 4) of that cycle.

A patient will be defined as "completed" if she completes Visit 4 (either as on-site visit or telephone contact) of Cycle 4. A patient will be defined as "completed cycle, not continuing" if she completes Visit 4 (either as on-site visit or telephone contact) of any cycle before Cycle 4 without continuing in the subsequent cycle. Study termination at a different time point other than Visit 4 of any cycle (including screening visit for one of the repeated cycles) will be considered as premature study discontinuation.

Overall study end date is defined as the date of last patient's last visit or telephone contact.

6.4 Premature Discontinuation

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

1. An AE occurs that, in the opinion of the Investigator, makes it unsafe for the patient to continue in the study.
2. The patient is lost to follow-up.
3. The patient dies.
4. The patient withdraws consent.
5. The Investigator, for any reason, terminates his/her participation in the study, or terminates the study for that patient; or the attending physician requests that the patient be withdrawn for any medical reason.
6. The Sponsor or the Regulatory Authorities or the Ethics Committee(s), for any reason, terminates the entire study, or terminates the study for this trial site or this particular patient.

Additionally to the above mentioned reasons, patients who successfully completed any of the study cycles may not continue to a subsequent study cycle for any of the following reasons:

- The patient is unwilling to participate in further chemotherapy cycles.
- The patient is no longer scheduled to receive any additional chemotherapy.

- The inclusion/exclusion criteria are no more satisfied for performing a repeated cycle
- The whole study is closed as per protocol definition.

If a patient is discontinued from the study after treatment with the investigational medicinal product, the Investigator must try his/her best to contact the patient 15 days after Day 1 of the last performed cycle in view of completing the study safety assessment by collecting information that may be suggestive of AEs.

Patients discontinued after randomization will not be replaced.

7 METHODS OF ASSESSMENT

7.1 Efficacy Assessments

Efficacy evaluations will be primarily based on the patients' documentation of emetic episodes (episodes of retching or vomiting), intake of rescue medication and nausea severity assessed daily by VAS during the period from 0 to 120 hours after the start of the AC chemotherapy administration on Day 1 of each cycle. To collect these data, a patient paper diary covering the 0-120 hours period after the start of AC chemotherapy, will be used.

In addition FLIE questionnaire covering the 5 days after start of AC chemotherapy will be collected during Cycle 1 and Cycle 2 only.

Given the precisely defined starting timepoint for the efficacy assessment period (i.e., the starting time of AC administration on Day 1) and the duration of such period (120 hours), the starting time and date of the AC chemotherapy infusion are to be carefully and precisely collected in the eCRF and reported on the patient diary to remind patient the correct time-frame of data to be collected in the diary.

The date of AC chemotherapy administration will determine study Day 1 and the starting time of its administration will define the study "time 0" for the assessment of time-related efficacy parameters.

Efficacy parameters will be evaluated in the overall, acute and delayed phases (time intervals 0 to 120 hours, 0 to 24 hours and >24 to 120 hours after the start of the AC chemotherapy administration, respectively).

For the detailed description of the efficacy endpoints see Section 3.1 Efficacy Endpoints.

7.1.1 Emetic Episodes

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). Emetic episodes are considered distinct if separated by absence of vomiting and retching for at least 1 minute. All patients will be asked to document in the patient diary all details about their emetic episodes occurring during the 120 hours after the start of AC chemotherapy administration.

These details will include:
- Each episode of retching or vomiting
- Date of each retching or vomiting episode
- Exact time of onset of each retching or vomiting episode.

Each emetic episode, as well as date and time of occurrence, will then be documented on the eCRF in accordance with the patient diary records.

7.1.2 Rescue Therapy

Rescue medication is defined in Section 5.15 Rescue Medication.

Rescue medication will be permitted on an as-needed basis. The patient will record in the patient diary the drug name, dosage and date/time of intake for each medication taken for the treatment of nausea and vomiting during the 0-120 hour interval (Day 1 to Day 5). Each rescue medication trade or generic name, dosage and route of administration, as well as the time and date of intake, will then be documented on the eCRF in accordance with the patient diary records.

7.1.3 Severity of Nausea

Severity of nausea will be evaluated by the patient in the patient diary for each day of the 0-120 hour interval (Days 1 to 5, inclusive), using a 100-mm horizontal VAS. The left end of the scale (0 mm) will be labeled as 'no nausea' and the right end of the scale (100 mm) will be labeled as 'nausea as bad as it could be'.

Each day starting from Day 2 and up to Day 6 of each cycle, the patient will be asked to record her assessment of the average degree of nausea during the preceding 24 hours ("How much nausea did you experience on average during the last 24 hours?"). The patient's assessment of the average severity of nausea in the preceding 24 hours will be performed by placing a vertical mark on the scale. Severity of nausea will then be documented on the eCRF in accordance with the patient diary records.

7.1.4 Functional Living Index-Emesis (FLIE) Questionnaire

The FLIE is a nausea and vomiting specific self report instrument comprised of two domains (nausea and vomiting) with nine identical items in each domain. FLIE was originally developed and validated to assess the impact on patient's daily life over the three days following chemotherapy. The measurement characteristics of the FLIE are also acceptable when administered with a 5-day recall period [14].

The items assess the impact of nausea and vomiting on multiple aspects of a patient's daily life. Each item is answered using a 100-mm (1 to 7 points) VAS with anchors corresponding to "none"/"not at all" and "a great deal". Items within the domain are weighted equally, reversed as required for some items (items with the scale anchors in the opposite direction) and summed to create the domain score according to the FLIE Scoring and Administration Manual. The two domain scores are then summed to create the total FLIE score. Higher FLIE scores indicate less impairment on daily life as a result of nausea and vomiting.

The FLIE questionnaire will be provided on paper to the patient during Visit 2 (Day 1) of Cycle 1 and Cycle 2, with adequate instructions on how to fill it. The patient will complete the FLIE questionnaire reflecting the impact of nausea and vomiting during the 5-day recall period after AC chemotherapy administration on Day 1.

The FLIE will then be collected and checked by the Investigator at Visit 3 (Day 6+2) of Cycle 1 and Cycle 2 and answers documented on the eCRF in accordance with the paper patient copy.

7.2 Safety Assessments

Safety is the primary objective of this study and will be assessed primarily by means of AEs collection and reporting. See Section 8 ADVERSE EVENTS for specific definitions. Additionally, details of other safety assessments are decribed in detail below.

7.2.1 Physical Examination

A complete physical examination will be performed at Visit 1 (screening) and at Visit 3 (Day 6 +2 days) of each cycle. 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. At Visit 3 and at subsequent cycles, only the general question "Was the physical examination performed?" will be asked on the eCRF.

Information about the physical examinations will be recorded in the source documentation at the site and any abnormalities at screening will be recorded in the eCRF. After signing the informed consent, any new or worsening of existing pathological findings noted since previous examination performed under the present protocol should be reported on the Adverse Event eCRF form.

7.2.2 Vital Signs

Vital signs assessments will include: pulse rate, systolic and diastolic blood pressure (at Visit 1, Visit 2 predose and Visit 3 of each cycle), height (Visit 2 of Cycle 1 only) and body weight (Visit 2 [Day 1 visit] of each cycle, at predose). Pulse rate, systolic and diastolic blood pressure will be measured after the patient has been resting in the semi-supine position for at least 5 minutes at Visit 1 (screening), Visit 2 (pre-dose i.e., before the oral NEPA FDC or matching placebo capsule administration) and Visit 3 (Day 6 + 2 days).

The following time windows will be applied for the measurement of vital signs:

- Visit 2 (Day 1 Visit), predose: within 30 minutes before oral NEPA FDC capsule or matching placebo capsule administration.
- Visit 3 (Day 6 +2 days visit): between 120 hours and 168 hours from start of AC administration on Day 1.

7.2.3 Clinical Laboratory Tests

At the screening visit for each cycle, the Investigator will be responsible to assess the adequacy of the patient to receive AC chemotherapy (see inclusion criteria), including laboratory parameters assessments. The following laboratory parameters will be assessed at Visit 1 and Visit 3 of each cycle using local laboratories:

- Hematology: hemoglobin, erythrocytes, leukocytes, platelets

- Blood Chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), bilirubin, alkaline phosphatase, creatinine and creatinine clearance (derived from blood creatinine value by application of the Cockcroft-Gault formula).

Females of childbearing potential will have to perform a urine (dipstick) pregnancy test at the Screening Visit and within 24 hours prior to the first dose (oral NEPA FDC or matching placebo capsule) of investigational drug administration at Day 1 of each cycle. In case the Screening Visit urine pregnancy test was performed within 24 hours prior to IMP, the urine test is not to be repeated on Day 1.

See Section 6.2 Study Procedures by Time Point and Study Flow Chart for additional details.

Upon receipt and after review, the Investigator must sign and date each local laboratory report and document in the relevant EDC form if the parameter is below, within or above normal ranges. The Investigator will review the values outside the normal range and repeat the test, if needed. In case clinically significant laboratory abnormalities are detected, 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.

Similarly, clinically significant laboratory abnormalities detected at Cycle 1 screening, if not justified by an underlying disease already recorded in the medical history, are to be recorded as AEs.

7.3 Health Economics Outcome Research (HEOR) Assessments

HEOR assessments in this study will include hospitalization information, lost work time, and details related to any changes in chemotherapy administration during the repeated cycles. Details of each are described in the sections below.

Additionally, other data collected from patient diary or eCRFs may also be used for HEOR-related analysis. All parameters of interest, endpoints and analysis methods will be pre-specified in a separate Health Economics Analysis Plan.

7.3.1 Work Productivity and Activity Impairment (WPAI) Questionnaire

The WPAI is a questionnaire used to document lost work time [15]. Actual lost work time (hours) will be recorded by patients on the WPAI and returned at Visit 3 (Day 6 +2 days), referring to the past five days since start of AC chemotherapy administration on Day 1. WPAI questionnaire will only be administered during Cycle 1 and Cycle 2.

7.3.2 Emergency Department (ED) Use and In-Patient (IP) Admissions

Patients will be asked dates of ED events and IP events. For each IP event, the length of stay in number of calendar days will be documented (i.e., minimum of 2). This information, referring to the interval from Visit 2 (Day 1) through Visit 4 of each cycle, will be recorded at Visit 4 of each cycle.

7.3.3 Subsequent Cycle Start Date and Changes from Initial Schedule

Starting at Cycle 2 Visit 2 (Day 1), the Investigator will document if changes in chemotherapy administration from the previous cycle occurred and will note any delays in treatment for the current cycle. If a subsequent cycle is not yet initiated by Visit 4, that shall be noted as well.

8 ADVERSE EVENTS

AE recording will begin at the time the informed consent form is signed until end of the study (completion/discontinuation), as a minimum. If the patient exit the study less than 15 days after last study drug administration, the patient should be followed-up for AEs recording up to 15 days after last study drug administration. AEs will be ascertained by asking the patient how she has been since the last visit.

8.1 Definition of Adverse Events

Adverse Event (AE)

As defined by the current ICH Guideline for Good Clinical Practice [16, 17] 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 had already signed the Informed Consent Form.

AEs include the following types of occurrences:

- Suspected adverse drug reactions
- Other medical experiences, regardless of their relationship to the study drugs, such as injury, surgery, accidents, increased severity of pre-existing symptoms, apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, physiological testing, or physical examination findings
- Reactions from drug overdose, abuse, withdrawal, hypersensitivity, or toxicity.

Planned procedures, surgical interventions or planned hospitalizations scheduled prior to the informed consent but performed during the study (study procedures, chemotherapy cycles, etc.) 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 treatment or meet the definition of serious AE.

Treatment-emergent adverse events (TEAEs) are defined as those AEs that start after the first study treatment administration on Day 1 of Cycle 1 until Visit 4 of the last study cycle.

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 Investigator's Brochure for IV NEPA FDC. [8]

Pre-existing Condition

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

8.1.1 Classification of Adverse Events

The Investigator will classify AEs based on their severity and relationship to IMP and dexamethasone. Every effort must be made by the Investigator to categorize each AE according to its severity (see Section 8.1.1.1 Severity), and its relationship (see Section 8.1.1.2 Relationship to Investigational Medicinal Product and Dexamethasone).

8.1.1.1 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) [18], 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.

8.1.1.2 Relationship to Investigational Medicinal Product and Dexamethasone

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

Definitely related

The event:
- Follows, in a reasonable temporal sequence, the administration of the drug or the drug level that has been established in body fluids or tissues.
- Follows a known or expected response pattern of the suspected drug.
- Is confirmed by improvement after de-challenge or dosage reduction of the drug.
- Reappears after repeated exposure (re-challenge).

Probably related

The event:
- Follows, in a reasonable temporal sequence, the administration of the drug.
- Follows a known or expected response pattern of the suspected drug.
- Is confirmed by improvement after de-challenge or dosage reduction of the drug.
- Cannot be reasonably explained by the known characteristics of the subject's clinical state.
- No re-challenge test or laboratory confirmation is available.

Possibly related

The event:
- Follows, in a reasonable temporal sequence, the administration of the drug.
- Follows a known or expected response pattern of the suspected drug but could have been easily produced by a number of other etiologies.

Unlikely related

There is no reasonable temporal association between the drug and the AE or the event could have been related to the subject's clinical state or concomitant treatment(s), or another cause adequately explaining the AE is known or is much more probable.

Not related / None

Sufficient information exists indicating that the etiology is unrelated to the drug.

Unassessable

The data are insufficient or contradictory to make a meaningful medical assessment. This criterion should be used only in case of insufficient evidence, conflicting data or poor documentation. Every effort should be done by the Investigator to make appropriate assessment of causal relationship (i.e., either related to the IMP, dexamethasone or both).

8.1.2 Reporting Adverse Events

AE reporting has to be in accordance with the ICH E6 Guidance on GCP and ICH E2A Guidance on Clinical Safety Management. [16, 17]

During the study, all AEs (including SAEs), irrespective of the relatedness to the study drugs, must be recorded in detail in the source records and transcribed onto the AEs pages of the eCRF. During each monitoring visit, the Investigator and 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.

In case clinically significant laboratory abnormalities are detected, the etiology of the abnormality should be identified and the diagnosis should be recorded as an AE. Otherwise, if the etiology can not be identified, the laboratory abnormality as such should be recorded as the AE.

Similarly, clinically significant laboratory abnormalities detected at the screening visit (before any administration of the investigational medicinal product or additional non-investigational drug), if not justified by an underlying disease already recorded in the medical history, are to be recorded as AEs.

The reporting period for AEs during the Study is the period starting from the time of Informed Consent signature and lasting until end of the study (completion/discontinuation), as a minimum. If the patient exit the study less than 15 days after last study drug administration, the patient should be followed-up for AEs recording up to 15 days after last study drug administration. All unresolved AEs (including SAEs) at the end of the reporting period will be documented on the eCRF as "ongoing".

8.1.3 Reporting Serious Adverse Events

All SAEs occurring from the time of signing of the informed consent until Visit 4 (either Day 15 +3 days or Day 22 ±3 days follow-up visit) of the last cycle, must be reported immediately to the CRO pharmacovigilance. Contact information is provided in the Investigator file as well as in the General Information Section of the present protocol. The Investigator or designated study coordinator must complete the Investigational Serious AE Form and send it to the CRO within 24 hours of observation or notification of a serious AE. 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 occurring during the Study, 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 the US Code of Federal Regulations 313.32, ICH E6 Guidance on GCP, and ICH E2A Guidance on Clinical Safety Management, will also be the responsibility of the Sponsor (or Sponsor's designee). [16, 17]

A safety contact sheet will be provided to the Investigator and will be maintained in the Investigator file at the site. Sites will be instructed to refer to the instructions and definitions for completing the Investigational SAE Form for submitting all SAEs to the CRO.

8.1.3.1 Follow-up of Serious Adverse Events

SAEs occurring during the study will be followed by the Investigator until the outcome is resolved, has reached a stable condition in the Investigator's opinion, or until the patient is lost to follow-up. When the investigational site receives any information about an SAE which changes or adds to the information on the initial investigational SAE form, the site will fill out a new investigational SAE form and tick the "follow-up" box of the SAE form and email it within 24 hours to the CRO.

8.1.4 Pregnancy Report

Female patients who are of childbearing potential must use an effective contraceptive/birth control measure while participating on study and have a negative urine pregnancy test at study entry. 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 e-mail address (see Section General Information). After check of consistency, designated personnel at the CRO will then forward the information to the Sponsor within 24 hours of becoming aware of the pregnancy. Even though pregnancy is not considered as SAE itself, pregnancy has to be reported within the timelines as defined for SAE.

Pregnant patients will be followed by the Investigator and CRO / Sponsor until the fetus / newborn is delivered or the pregnancy is terminated. The subject's primary care physician (or obstetrician) will be requested by the Investigator to provide further information on the pregnancy using the Pregnancy Outcome Information Form. At the study end and database closure, reports of Pregnancy Outcome will be sent by the sites directly to Helsinn Drug Safety.

9 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 [19].

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 breaking the blind. Changes from analyses planned in this protocol will be documented in the SAP and/or study report. The database will be locked after all queries are resolved, and a blinded review of data is performed and decisions made about study populations and handling of unused or missing data.

9.1 Sample Size Determination

A total of 400 patients will be randomized, equally distributed in two groups (i.e., 200 patients/group).

Patients will be randomized according to a randomization ratio 1:1, stratified by region and age class.

The primary goal of this study is to characterize the safety profile of IV NEPA FDC over a reasonable duration of time consistent with the intended use of this drug. Although no formal comparison is planned with the randomized control group, the presence of a concurrent control group in the same patient population may help interpret any unexpected safety finding in the test group.

9.2 Definition of Study Populations for Analysis

Study populations are defined as follows:

The **Full Analysis Set (FAS)** includes all patients who have been randomized to treatment and received AC chemotherapy regimen and active study drug (oral NEPA FDC or IV NEPA FDC, including partial infusion). Following the intent-to-treat principle, patients will be assigned to the study treatment group according to the treatment to which they have been randomized.

FAS will be used for demography, other baseline characteristics, all descriptive efficacy analyses.

The **Safety population** includes all patients who received active study drug (oral NEPA FDC or IV NEPA FDC, including partial infusion). Patients will be assigned to study treatment groups according to the actual treatment received.

Safety population will be used for demography, other baseline characteristics and for all safety analyses.

9.3 Statistical Analysis

9.3.1 General Considerations

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

9.3.1.1 Missing Data

Due to the short efficacy assessment period within each study cycle (a maximum of 120 h considering all the efficacy assessments), a very low number of drop-outs and minimal missing data is expected during the cycle.

For efficacy analyses, any patient who does not provide data about occurrence of emetic episodes and rescue medication intake is to be considered as treatment failure (i.e., non-responder) for CR in the overall phase. The same approach is to be applied also to CR in the acute and delayed phases. For consistency, the same approach for handling missing data as described for CR will also to be applied to emetic episodes and rescue medication intake.

For safety analyses, no imputations will be performed on missing values.

Since there might be cases where emetic episodes and rescue medications intake in the 0-120 hours from start of AC chemotherapy are, by mistake, recorded in the eCRF Adverse Events and Prior and Concomitant medications form only (and not in the patient diary), in accordance with the definition of CR, such cases will be taken into account for efficacy analyses and patients considered as failures.

For nausea intensity data collected daily, missing values in the 0-24 hour interval or missing data preceding any available data will be replaced using the worst case principle i.e., using the highest value observed in the same treatment and time interval among all patients with the same stratifications factors (i.e., region, age class and naivety). Missing data after at least one available value will be replaced using Last Observation Carried Forward (LOCF). The worst value will be evaluated after applying LOCF to other missing data.

Patients with no nausea and with no significant nausea will be then derived from the complete data after imputation of missing data.

Concerning the FLIE scores, for the purpose of calculating the score for a domain (either nausea or vomiting), at least 5 of the 9 FLIE items (i.e., > 50% overall item response rate) in the domain must be non-missing. The score, expressed in mm, of each domain will be calculated as:

$$\text{Domain score (in mm)} = \frac{\sum \text{item scores (in mm)}}{\text{no. items answered}} \times 9$$

To obtain the score expressed in FLIE points, the above mentioned domain score expressed in mm is multiplied by 0.06, as a final step 9 will then be added.

$$\text{Domain score (in FLIE points)} = (\text{Domain score (in mm)} \times 0.06) + 9$$

For the calculation of the total FLIE score (i.e., sum of the nausea and vomiting domain scores), at least 12 out of the 18 FLIE items (i.e., ≥ 66% overall item response rate) must be non-missing and both the vomiting and nausea domains must be non-missing.

A missing single item will not be replaced. A missing entire domain score will be replaced using the worst case principle i.e., using the lowest score observed in the same treatment among all patients with same age class. The total FLIE score will be then calculated from the complete data after imputation of missing data.

9.3.1.2 Multiplicity

Since no formal comparisons between treatments are planned, no multiplicity adjustment is foreseen.

9.3.1.3 Covariates, Interactions and Subgroups

It is expected that region (US, non-US) and age class (<55 years, ≥55 years) could influence the study endpoints. For this reason, these factors will be taken into consideration for randomization (see Section 5.11 Randomization - Use of IWRS) so to minimize possible unbalance between groups.

Selected efficacy endpoints at Cycle 1 (CR in the acute, delayed and overall phases) will be also summarized by region and by age group.

9.3.2 Analysis of Demographics and Baseline Variables

Demographics and baseline variables will be summarized by treatment arm using descriptive statistics.

9.3.3 Efficacy Analysis

Analyses of efficacy endpoints will be performed on FAS.

All results will be interpreted in descriptive manner only.

At each cycle, for each phase (acute, delayed, and overall), numbers and proportions (including 95% CI using Wilson score method) of patients with CR, with no emetic episodes, with no rescue medication, with no nausea, and with no significant nausea will be descriptively summarized.

In addition, for Cycle 1, CR in the acute, delay and overall phases will be summarized by region and by age group (strata).

Since VAS is assessed daily, for no significant nausea and no nausea in the delayed and overall phases, the maximum VAS value in the relevant phase will be considered (i.e., the

maximum value for Day 2 to 5 for delayed phase and for Day 1 to 5 for the overall phase).

For the above mentioned variables, differences between groups will be presented using the CMH method for the risk difference (including region and age class as strata) and relative two-sided 95% CI. The treatment difference and 95% CI for the difference will also be presented without strata adjustment, using the Newcombe-Wilson's method.

The severity of nausea in the acute, delayed and overall phase, will be descriptively summarized including treatment difference and relative two-sided 95% CI.

Antiemetic rescue medications will be tabulated by treatment arm.

In Cycle 1 and Cycle 2, only, to assess the impact of nausea and vomiting on patients' quality of life, the FLIE with a 5-day recall will be used. A total FLIE score (expressed in FLIE points) greater than 108 will be categorized as having No Impact on Daily Life (NIDL) [14]. A FLIE domain score (either nausea or vomiting, expressed in FLIE points) greater than 54 will be categorized as NIDL [14]. A response to an individual question on the FLIE will be categorized as NIDL if the score expressed in FLIE points is greater than 6.

Number and percentage (including 95% CI) of patients with NIDL (overall, by domain and by individual item), will be summarized by treatment. Differences between groups for total FLIE score and domain scores (nausea and vomiting) will be presented using the CMH method for the risk difference and relative two-sided 95% CI. The treatment difference and 95% CI will also be presented without strata adjustment.

The mean nausea and vomiting domain FLIE scores and the mean total score will be will be descriptively summarized including treatment difference and relative two-sided 95% CI.

9.3.4 Safety Analysis

The safety analysis will be performed on the Safety population.

Clinical evaluations for safety assessments will include physical examinations, vital signs, and laboratory tests during each cycle (Visit 1 through Visit 4), and monitoring of AEs through the study period.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary (the version will be provided in the SAP and in the Data Management Plan [DMP]) to give a preferred term (PT) and a system organ class (SOC) for each event. The number and percentage of patients who experienced at least one TEAE, drug-related TEAE (defined as AEs with relationship classified by the investigator as definitely, probably, possibly, unassessable or missing), serious TEAE, serious related, severe TEAE (i.e., TEAE with CTCAE grade ≥ 3) and the number and percentage of patients withdrawn due to TEAE will be summarized by treatment arm. Summaries will be made with respect to the proportion of patients with events and the total number of events throughout the study. A similar summary will be presented for Cycle 1 only.

For each SOC and PT, summaries will be made with respect to the proportion of patients having at least one occurrence of that event during the study and the total number of events. The incidence of TEAEs in each treatment arm will be presented overall, by SOC and PT, and by additional grouping by severity according to the CTCAE grade and relationship to the study treatment. Tables of TEAEs will be presented by relationship to study drug and to dexamethasone. Additional tables including any relationship (either to study drug or dexamethasone) will be presented. Summary will be presented considering all the performed cycles (i.e., throughout the study) and for Cycle 1, only.

In addition, TEAEs of special interest, i.e. the ones related to local tolerability (e.g. injection site reaction, pain at injection site, thrombophlebitis) will be summarized for each cycle.

No formal test will be used for "between groups" comparison. All AEs will be listed. Pre-treatment AEs will be listed separately from TEAEs.

Vital signs will be summarized by treatment using descriptive statistics for absolute values, change from baseline (i.e., last value before first study drug intake), and change from pre-dose assessment of each cycle in addition to being listed.

Physical examination results at screening will be summarized in a frequency table (normal/abnormal). Results and relevant findings will be listed.

Proportion of laboratory values below, within and above normal range will be presented by frequency table for each timepoint. Shift table (below, within and above normal range) comparing baseline (i.e., last value before first study drug intake) assessment with on-treatment assessment and comparing pre-dose assessment with Visit 3 assessment of each cycle will also presented.

9.3.5 HEOR Analysis

The HEOR analysis will be managed and conducted separately. Relevant patient data and results will be presented in a separate dedicated report. Further details (including detailed description of HEOR endpoints and analyses) will be outlined in the Health Economics Analysis Plan.

9.4 Interim Analysis

No formal interim analysis is planned for this study.

Descriptive statistics of data elements from exploratory HEOR assessments may be calculated on blinded data at intervals to-be-determined based on study enrollment. Data from a minimum of 50 patients will be available prior to creating this summary.

10 DATA SAFETY MONITORING BOARD

No data safety monitoring board is planned for this study.

11 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Ethical Considerations

The study will be performed in accordance with the principles outlined in the Declaration of Helsinki [23] 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 countries in which the study is conducted.

11.1.1 Laws and Regulations

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

11.1.2 Patient's Information Sheet and Informed Consent Form

All patients invited to participate in the clinical trial are entitled to make their decision based on all current available information provided to them by the Investigator/designee. In addition, they will be given a document in native language written in clear concise lay language for review and consideration. The document will previously have been approved by relevant independent Ethics Committee(s) (EC[s]/Institutional Review Boards [IRBs]) and may further be updated as new important information becomes available that may affect subject's willingness to participate or continue in the trial. This document will tell potentially eligible subjects about the nature of the study drugs, their efficacy and safety profile, the route of administration, and the human experience available. It will also outline the steps of the protocol as they will apply to the individual, including the number of visits and types of procedures/assessments/measurements to be performed so that the individual has a clear picture of the risks, inconveniences and benefits that may accrue from the trial. The patient must be made aware that she may refuse to join the trial or may withdraw her consent at any time without prejudicing further medical care and that she is covered by the Sponsor's indemnity insurance in the event of a trial related injury. Contact details to report and discuss suspected trial-related injuries will be provided. Patients must also know that their personal medical records may be reviewed in confidence by the Sponsor's staff or representatives and by Regulatory Authorities and IRB/EC and that personal information will be collected and retained in a confidential database. Conditions for ensuring the anonymity of data and the security and confidentiality of the database should be explained. Consent will always be given in writing after the patient has had adequate time to review the information and ask questions, if need be. The patient and the Investigator or responsible site staff member conducting the informed consent discussion will both personally write their name, sign and date the consent form. Patients will be given a copy of their executed informed

consent. The study is being performed in the United States, Russia, Ukraine, and Georgia. US maintain descriptions of clinical studies in the participating countries on the internet. As required by the US FDA, the informed consent form must contain the following text: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

11.1.3 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 IRB/EC for review and approval unless it covers administrative issues only. In this case, the IRB/EC will be notified of the amendment for information purposes only.

11.1.4 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 subjects.

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

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

11.1.5 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.

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.

Queries will be used to validate/clarify data entered on an eCRF page. Some queries 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, others will be created manually in the

system and sent either by the study monitor (as result of Source Data Verification) or by Clinical Data Management.

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 query 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. 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.

Laboratory values will be assessed according to local laboratories normal ranges. Assessments (below, within and above normal range) will be reported directly into the eCRF by the study personnel. All data will be checked by the monitor.

Paper patient diaries will be used to collect emetic episodes (i.e., retching and vomiting episodes), rescue medication intake and daily nausea assessment. Taking into account the patient population, the short re-call period (i.e., 120 hours for efficacy endpoints) and the fact that rescue medication intake and emetic episodes are objective data, the paper diary is considered to be a reliable method of data collection and the most suitable for this patient population. The Investigator will review the filled in paper diary at Visit 3 (Day 6+2) of each cycle and discuss with the patient any issues or missing/incomplete data, so that the patient makes all necessary corrections, if any, during the visit. The Investigator or designee will review, sign, date and collect the complete patient diaries after it is returned at Visit 3 of each cycle and will also transfer all data from the paper diary to the eCRF. The paper diaries will be kept at the trial site and considered as source documents.

A paper FLIE questionnaire with a 5-day recall period will be used to assess the impact of nausea and vomiting on patients' quality of life. The FLIE questionnaire will be filled in by the patient on Day 6 of Cycle 1 and Cycle 2, covering the past 5 days and checked and retrieved by the Investigator during study Visit 3 (Day 6+2) of Cycle 1 and Cycle 2. FLIE data will be then reported in the relevant eCRF page by the Investigator.

Additional HEOR-related assessments will also be captured. Emergency department, in-patient admissions and length of stay will be documented by the Investigator or designated responsible person at Visit 4 of each cycle for events occurring since Day 1 of that cycle. Additionally, starting at Cycle 2 Visit 2 (Day 1), the Investigator will document if changes in chemotherapy administration from the previous cycle occurred and will note any delays in treatment for the current cycle.

A paper WPAI questionnaire with a 5-day recall period will be used to assess the effect of CINV on patients' ability to work and perform regular activities, including documentation of lost work time. The WPAI questionnaire will be filled in by the patient on Day 6 of Cycle 1 and Cycle 2, covering the past 5 days and checked and retrieved by

the Investigator during study Visit 3 (Day 6 +2 days) of Cycle 1 and Cycle 2. WPAI data will be then reported in the relevant eCRF page by the Investigator.

11.1.6 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, Good Clinical Practice guideline and applicable regulatory requirements. During the monitoring visits, monitors will verify the following including but not limited to: patient informed consent, 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 may 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.

11.1.7 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 should be retained at the sites until when the Sponsor informs the Investigators/institutions in writing about 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 [15]. Should the Investigator wish to assign

the study documentation to another party or move to another location, the Sponsor should promptly be notified.

11.1.8 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 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.

11.1.9 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).

11.1.10 Insurance

The Sponsor/designee will obtain liability insurance, which covers health impairments resulting from drugs and/or substances/investigational products administered in the course of this study for which the patient has given his/her written informed consent. This liability insurance also covers health impairments resulting from study procedures.

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13 APPENDICES

Appendix 1: Emetogenic Potential of IV and Oral Antineoplastic Agents (NCCN Clinical Practice Guidelines in Oncology, Version 2.2017, March 28, 2017)

Appendix 2: Eastern Cooperative Oncology Group Performance Status (ECOG PS)

Appendix 3: List of CYP3A4 Inducers, Strong and Doderate Inhibitors, and Substrates

Appendix 1: Emetogenic Potential of IV and Oral Antineoplastic Agents (NCCN Clinical Practice Guidelines in Oncology, Version 2.2017, March 28, 2017 [7])

Emetogenicity Level	IV Agents[a, b]
High (>90% frequency of emesis[c])	AC combination defined as any chemotherapy regimen that contains anthracycline and cyclophosphamide Carboplatin AUC ≥ 4 Carmustine > 250 mg/m^2 Cisplatin Cyclophosphamide ≥1500 mg/m^2 Dacarbazine Doxorubicin ≥ 60 mg/m^2 Epirubicin >90 mg/m^2 Ifosfamide ≥ 2 g/m^2 per dose Mechlorethamine Streptozocin
Moderate (>30%-90% frequency of emesis[c])	Alemtuzumab >12-15 million IU/m^2 Amifostine > 300 mg/m^2 Arsenic trioxide Azacitidine Bendamustine Busulfan Carboplatin AUC <4[d] Carmustine ≤ 250 mg/m^2 Clofarabine Cyclophosphamide ≤ 1500 mg/m^2 Cytarabine >200 mg/m^2 Dactinomycin[d] Daunorubicin[d] Dinutuximab Doxorubicin [d] < 60 mg/m^2 Epirubicin [d] ≤ 90 mg/m^2 Idarubicin Ifosfamide [d] < 2 g/m^2 per dose Interferon alfa ≥ 10 million IU/m^2 Irinotecan [d] Melphalan Methotrexate [d] ≥ 250 mg/m^2 Oxaliplatin [d] Temozolomide Trabectedin [d]

Emetogenicity Level	IV Agents[a, b]
Low (10%-30% frequency of emesis[c])	Ado-trastuzumab emtansine Aldesleukin ≤ 12 million IU/m^2 Amifostine ≤ 300 mg/m^2 Atezolizumab Belinostat Blinatumomab Brentuximab vedotin Cabazitaxel Carfilzomib Cytarabine (low dose) 100-200 mg/m^2 Docetaxel Doxorubicin (liposomal) Eribulin Etoposide 5-Fluorouracil Floxuridine Gemcitabine Interferon alfa > 5- <10 million IU/m^2 Irinotecan (liposomal) Ixabepilone Methotrexate > 50 mg/m^2 - <250 mg/m^2 Mitomycin Mitoxantrone Necitumumab Omacetaxine Paclitaxel Paclitaxel-albumin Pemetrexed Pentostatin Pralatrexate Romidepsin Talimogene laherparepvec Thiotepa Topotecan Ziv-aflibercept

Emetogenicity Level	IV Agents[a, b]
Minimal (<10% frequency of emesis[c])	Alemtuzumab Asparaginase Bevacizumab Bleomycin Bortezomib Cetuximab Cladribine (2-chlorodeoxyadenosine) Cytarabine < 100 mg/m^2 Daratumumab Decitabine Denileukin diftitox Dexrazoxane Elotuzumab Fludarabine Interferon alpha ≤ 5 million IU/m^2 Ipilimumab Methotrexate ≤ 50 mg/m^2 Nelarabine Nivolumab Obinutuzumab Ofatumumab Panitumumab Pegaspargase Peginterferon Pembrolizumab Pertuzumab Ramucirumab Rituximab Siltuxumab Temsirolimus Trastuzumab Valrubicin Vinblastine Vincristine Vincristine (liposomal) Vinorelbine

a) Continuous infusion may make an agent less emetogenic.
b) Potential drug interactions between antineoplastic agents/antiemetic therapies and various other drugs should always be considered.
c) Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.
d) These agents may be highly emetogenic in certain patients.

Emetogenicity Level	Oral Agents[a]	
Moderate to High (≥30% frequency of emesis[b])	Altretamine Busulfan (≥4 mg/d) Ceritinib Crizotinib Cyclophosphamide (≥100 mg/m^2/d) Estramustine Etoposide Lenvatinib Lomustine (single day) Mitotane	
Minimal to Low (<30% frequency of emesis[b])	Afatinib Alectinib Axitinib Bexarotene Bosutinib Busulfan (<4 mg/d) Cabozantinib Capecitabine Chlorambucil Cobimetinib Cyclophosphamide (<100 mg/m^2/d) Dasatinib Dabrafenib Erlotinib Everolimus Fludarabine Gefitinib Hydroxyurea Ibrutinib Idelalisib Imatinib Ixazomib Lapatinib	Lenalidomide Melphan Mercaptopurine Methotrexate Nilotinib Osimertinib Palbociclib Pazopanib Pomalidomide Ponatinib Regorafenib Ruxolitinib Sonidegib Sorafenib Sunitinib Temozolomide (≤75 mg/m^2/d) Thalidomide Thioguanine Topotecan Tretinoin Vandetanib Venetoclax Vismodegib Vorinostat

a) Potential drug interactions between antineoplastic agents/antiemetic therapies and various other drugs should always be considered.

b) Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.

Appendix 2: 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 ClinOncol 5:649-655; 1982. [24]

Appendix 3: List of CYP3A4 Inducers, Strong and Moderate Inhibitors, and Substrates

Examples of inducers, strong and moderate inhibitors, and Substrates of CYP 3A4	
Type	Agent
Inducers	HIV Antivirals: efavirenz, nevirapine, barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone
Strong and moderate Inhibitors	**Strong inhibitors:** A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold. Strong Inhibitors are: Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole **Moderate inhibitors:** A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold. Moderate Inhibitors are: Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, miconazole, fosamprenavir, grapefruit juice, imatinib, verapamil, atazanavir, amiodarone
Substrates	Terfenadine, cisapride, astemizole, pimozide

For strong and moderate inhibitors of CYP3A, see
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Study Title

A multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group phase 3b study to assess the safety and to describe the efficacy of IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) compared to oral netupitant/palonosetron (300 mg/0.5 mg) combination (Akynzeo®) for the prevention of chemotherapy-induced nausea and vomiting in initial and repeated cycles of anthracycline-cyclophosphamide (AC) chemotherapy in women with breast cancer

Study Number	NEPA-17-05
Protocol Date	22 Jun 2017
Protocol Amendment #1 (v2.0)	14 Sep 2017
Protocol Amendment #2 (v3.0)	14 Nov 2017
Protocol Amendment # 3 (v3.1)	30 Nov 2017
Sponsor	Helsinn Healthcare SA Via Pian Scairolo 9 6912 Lugano, Switzerland
CROs	US Region: George Clinical Inc. 6555 Quince, Suite 503 Memphis, TN 38119 Phone: +1 901.259.0888 Fax: +1 901.259.8276 Europe: PSI CRO AG Baarerstrasse 113a 6300 Zug, Switzerland Phone: +41 41 228 10 00 Fax: +41 41 228 10 99

Confidential Information

The information contained in this document is confidential. Acceptance of this document constitutes agreement by the recipient that no information contained herein will be published or disclosed without prior written authorization from an official of Helsinn except that this document may be disclosed to appropriate Institutional Review Boards and Ethics Committees or duly authorized representatives of a Regulatory Authority under the condition that they are requested to keep it confidential.

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 EU Clinical Trials Directive 2001/20/EC and ICH Guideline for Good Clinical Practice.

Signature Page, Helsinn Healthcare SA

Medical Expert:

[redacted]

4 DEC 2017
(Date)

Head of Clinical Development

Study Coordinator:

[redacted]

4 Dec 2017
(Date)

Clinical Operations Manager, Clinical Development

Statistician:

[redacted]

4 DEC 2017
(Date)

Statistician and Data Manager, Clinical Development

Drug Safety Officer:

[redacted]

04/12/2017
(Date)

Head of Drug Safety

Medical Writer:

[redacted]

04/DEC/2017
(Date)

Senior Clinical Research Scientist, Clincial Research & Strategy

Signature Page, George Clinical Inc.

Project Manager:

_____ 05 Dec 2017

(Signature) (Date)

[redacted] MSc
Project Manager

Signature Page, PSI

Project Manager:

[redacted] 06-Dec-2017

(Date)

Project Manager

Signature Page, Study Site Investigator

Study Title

A multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group phase 3b study to assess safety and to describe the efficacy of IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) compared to oral netupitant/palonosetron (300 mg/0.5 mg) combination (Akynzeo®) for the prevention of chemotherapy-induced nausea and vomiting in initial and repeated cycles of anthracycline-cyclophosphamide (AC) chemotherapy in women with breast cancer

Study Number NEPA-17-05

I have read and understood all pages of Protocol Amendment #3 and agree to abide by all the conditions and instructions contained therein.

_____ _____

(Signature) (Date)

Printed Name:

Institution:

1 REASONS FOR AMENDMENT

A new protocol version v3.1 dated 30 Nov 2017 is issued to revise the protocol final version v3.0 dated 14 Nov 2017.

With respect to v3.0, in v3.1 minor typing errors have been corrected in the numbering sequence of Exclusion criteria in Section 4.3.3 Exclusion criteria, steps in Section 5.4 Dose and Administration, and reasons for discontinuations in Section 6.4 Premature Discontinuation. Study title on coverpage was also corrected as "nausea" was inadvertently omitted and the main phone number for George Clinical was updated. Detail about study drug administration was added to Section 5.9 Administration of Study Treatment.

2 SITES TO WHICH THE AMENDMENT IS APPLICABLE

This Amendment #3 is applicable to all sites in the study.

3 LIST OF CHANGES

Specific changes to the protocol are as follows. Amended text is struck through (~~xxx~~), where appropriate, to aid identification of text deletion, while added new text is in *italic font, underlined*.

The final new text is reported in *italic font* under "Now reads".

4 PROTOCOL CHANGES

Section: Study Title

Amended text:

"**Study Title**

A multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group phase 3b study to assess the safety and to describe the efficacy of IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) compared to oral netupitant/palonosetron (300 mg/0.5 mg) combination (Akynzeo®) for the prevention of chemotherapy-induced *nausea* and vomiting in initial and repeated cycles of anthracycline-cyclophosphamide (AC) chemotherapy in women with breast cancer"

Now reads:

"**Study Title**

A multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group phase 3b study to assess the safety and to describe the efficacy of IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) compared to oral netupitant/palonosetron (300 mg/0.5 mg) combination (Akynzeo®) for the prevention of chemotherapy-induced *nausea* and vomiting in initial and repeated cycles of anthracycline-cyclophosphamide (AC) chemotherapy in women with breast cancer"

Reason: To align with correction made to the study protocol title.

Section: COVER PAGE AND GENERAL INFORMATION

Amended text:

CROs:

US Region: George Clinical Inc., 6555 Quince, Suite 503, Memphis, TN 38119
Phone: ~~+1 901.435.5570~~; Phone: *+1 901.259.0888*

Now reads:

CROs*:*

US Region: George Clinical Inc., 6555 Quince, Suite 503, Memphis, TN 38119
Phone: *+1 901.259.0888*

Reason: To align with updated phone number for George Clinical.

Section 4. STUDY PLAN: 4.3 Study Population

4.3.3 Exclusion Criteria

Amended text:

"Cycle 1:

The following exclusion criteria must be checked prior to inclusion at Cycle 1:

~~5~~*1*. Lactating patient.

~~6~~*2*. Current use of illicit drugs or current evidence of alcohol abuse.

~~7~~*3*. Scheduled to receive moderately or highly emetogenic antineoplastic agent (see protocol Appendix 1) in addition to the AC regimen, from 6 hours after the start of the AC chemotherapy on Day 1 and up to Day 1 of Cycle 2.

~~8~~*4*. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of AC chemotherapy administration on Day 1 or between Days 1 to 5, inclusive.

~~9~~5. Any vomiting, retching, or nausea (grade • 1 as defined by National Cancer Institute) within 24 hours prior to the start of AC chemotherapy administration on Day 1.

~~10~~6. Symptomatic primary or metastatic central nervous system (CNS) malignancy.

~~11~~7. Active peptic ulcer disease, gastrointestinal obstruction, increased intracranial pressure, hypercalcemia, an active infection or any illness or medical conditions (other than malignancy) that, in the opinion of the Investigator, may confound the results of the study, represent another potential etiology for emesis and nausea (other than CINV) or pose unwarranted risks in administering the study drugs to the patient.

~~12~~8. Known hypersensitivity or contraindication to 5-HT3 receptor antagonists (e.g., palonosetron, ondansetron, granisetron, dolasetron, tropisetron, ramosetron), to dexamethasone, or to NK1 receptor antagonists (e.g., aprepitant, rolapitant).

~~13~~9. Known contraindication to the IV administration of 50 mL 5% glucose solution.

~~14~~10. Participation in a previous clinical trial involving IV fosnetupitant or oral netupitant administered alone or in combination with palonosetron.

~~15~~11. Any investigational drugs taken within 4 weeks prior to Day 1, and/or is scheduled to receive any investigational drug (other than those planned by the study protocol) during the present study.

~~16~~12. Systemic corticosteroid therapy within 72 hours prior to the start of AC chemotherapy administration on Day 1, except the dexamethasone provided as additional study drug. However, topical and inhaled corticosteroids are permitted.

~~17~~13. Scheduled to receive bone marrow transplantation and/or stem cell rescue therapy during the study participation.

~~18~~14. Other than as administered as part of the study protocol, any medication with known or potential antiemetic activity within 24 hours prior to the start of AC chemotherapy administration on Day 1, including:

- 5-HT3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron, tropisetron, ramosetron, palonosetron)
- NK1 receptor antagonists (e.g., fosaprepitant, aprepitant, rolapitant or any other new drug of this class)
- benzamides (e.g., metoclopramide, alizapride)
- phenothiazines (e.g., prochlorperazine, promethazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine)
- benzodiazepines (except if the subject is receiving such medication for sleep or anxiety and has been on a stable dose for at least seven days prior to Day 1).
- butyrophenones (e.g., haloperidol, droperidol)
- anticholinergics (e.g., scopolamine, with the exception of inhaled anticholinergics for respiratory disorders, e.g., ipratropium bromide)

- antihistamines (e.g., cyclizine, hydroxyzine, diphenhydramine, chlorpheniramine)
- domperidone
- mirtazapine
- olanzapine
- prescribed cannabinoids (e.g., tetrahydrocannabinol or nabilone)
- Over The Counter (OTC) antiemetics, OTC cold or OTC allergy medications.

~~19~~*15*. Scheduled to receive any strong or moderate inhibitor of CYP3A4 (see protocol Appendix 3) during the efficacy assessment period (Day 1 to Day 5, inclusive) or its intake within 1 week prior to Day 1.

~~20~~*16*. Scheduled to receive any CYP3A4 inducer (see protocol Appendix 3) during the efficacy assessment period (Day 1 to Day 5, inclusive) or its intake within 4 weeks prior to Day 1, with the exception of corticosteroids (for which exclusion criterion #12 applies).

~~21~~*17*. History or predisposition to cardiac conduction abnormalities, except for incomplete right bundle branch block.

~~22~~*18*. History of risk factors for Torsades de Pointes (heart failure, hypokalemia, family history of Long QT Syndrome).

~~23~~*19*. Severe or uncontrolled cardiovascular diseases, including myocardial infarction within 3 months prior to Day 1, unstable angina pectoris, significant valvular or pericardial disease, history of ventricular tachycardia, symptomatic Congestive Heart Failure (CHF) New York Heart Association (NYHA) class III-IV, and severe uncontrolled arterial hypertension.

All exclusion criteria with the exception of criteria #5, #12, and #14 will be checked at screening visit (Visit 1). Exclusion criteria #5, #12, and #14 will be checked at Day 1 (Visit 2) only. Exclusion criteria #3, #4, #11, #13, #15, and #16 need to be re-checked at Day 1 (Visit 2).

Cycles 2 to 4:

The following exclusion criteria must be checked prior to inclusion at each repeated cycle:

~~24~~*1*. Scheduled to receive moderately or highly emetogenic antineoplastic agent (see protocol Appendix 1) in addition to the AC regimen, from 6 hours after the start of the AC chemotherapy on Day 1 of current cycle and up to Day 1 of the next cycle.

~~25~~*2*. Active infection or uncontrolled disease that may pose unwarranted risks in administering the study drugs to the patient.

~~26~~*3*. Started any of the prohibited medications (see protocol Section 5.14).

~~27~~*4*. Any vomiting, retching, or nausea (grade ≥ 1 as defined by National Cancer Institute) within 24 hours prior to the start of AC chemotherapy administration on Day 1.

~~28~~5. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of AC chemotherapy administration on Day 1 or between Days 1 to 5.

~~29~~6. Symptomatic primary or metastatic CNS malignancy.

~~30~~7. Any illness or medical condition that, in the opinion of the investigator, may confound the results of the study or pose unwarranted risks in administering the investigational product or dexamethasone to the patient.

All exclusion criteria, with exception of criterion #4, will be checked at screening visit (Visit 1). Exclusion criterion #4 will be checked at Day 1 (Visit 2) only. Exclusion criteria #2, #3 and #5 need to be re-checked at Day 1 (Visit 2)."

Now reads:

"Cycle 1:

The following exclusion criteria must be checked prior to inclusion at Cycle 1:

1. Lactating patient.

2. Current use of illicit drugs or current evidence of alcohol abuse.

3. Scheduled to receive moderately or highly emetogenic antineoplastic agent (see protocol Appendix 1) in addition to the AC regimen, from 6 hours after the start of the AC chemotherapy on Day 1 and up to Day 1 of Cycle 2.

4. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of AC chemotherapy administration on Day 1 or between Days 1 to 5, inclusive.

5. Any vomiting, retching, or nausea (grade • 1 as defined by National Cancer Institute) within 24 hours prior to the start of AC chemotherapy administration on Day 1.

6. Symptomatic primary or metastatic central nervous system (CNS) malignancy.

7. Active peptic ulcer disease, gastrointestinal obstruction, increased intracranial pressure, hypercalcemia, an active infection or any illness or medical conditions (other than malignancy) that, in the opinion of the Investigator, may confound the results of the study, represent another potential etiology for emesis and nausea (other than CINV) or pose unwarranted risks in administering the study drugs to the patient.

8. Known hypersensitivity or contraindication to 5-HT3 receptor antagonists (e.g., palonosetron, ondansetron, granisetron, dolasetron, tropisetron, ramosetron), to dexamethasone, or to NK1 receptor antagonists (e.g., aprepitant, rolapitant).

9. Known contraindication to the IV administration of 50 mL 5% glucose solution.

10. Participation in a previous clinical trial involving IV fosnetupitant or oral netupitant administered alone or in combination with palonosetron.

11. Any investigational drugs taken within 4 weeks prior to Day 1, and/or is scheduled to receive any investigational drug (other than those planned by the study protocol) during the present study.

12. Systemic corticosteroid therapy within 72 hours prior to the start of AC chemotherapy administration on Day 1, except the dexamethasone provided as additional study drug. However, topical and inhaled corticosteroids are permitted.

13. Scheduled to receive bone marrow transplantation and/or stem cell rescue therapy during the study participation.

14. Other than as administered as part of the study protocol, any medication with known or potential antiemetic activity within 24 hours prior to the start of AC chemotherapy administration on Day 1, including:

- 5-HT3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron, tropisetron, ramosetron, palonosetron)
- NK1 receptor antagonists (e.g., fosaprepitant, aprepitant, rolapitant or any other new drug of this class)
- benzamides (e.g., metoclopramide, alizapride)
- phenothiazines (e.g., prochlorperazine, promethazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine)
- benzodiazepines (except if the subject is receiving such medication for sleep or anxiety and has been on a stable dose for at least seven days prior to Day 1).
- butyrophenones (e.g., haloperidol, droperidol)
- anticholinergics (e.g., scopolamine, with the exception of inhaled anticholinergics for respiratory disorders, e.g., ipratropium bromide)
- antihistamines (e.g., cyclizine, hydroxyzine, diphenhydramine, chlorpheniramine)
- domperidone
- mirtazapine
- olanzapine
- prescribed cannabinoids (e.g., tetrahydrocannabinol or nabilone)
- Over The Counter (OTC) antiemetics, OTC cold or OTC allergy medications.

15. Scheduled to receive any strong or moderate inhibitor of CYP3A4 (see protocol Appendix 3) during the efficacy assessment period (Day 1 to Day 5, inclusive) or its intake within 1 week prior to Day 1.

16. Scheduled to receive any CYP3A4 inducer (see protocol Appendix 3) during the efficacy assessment period (Day 1 to Day 5, inclusive) or its intake within 4 weeks prior to Day 1, with the exception of corticosteroids (for which exclusion criterion #12 applies).

17. History or predisposition to cardiac conduction abnormalities, except for incomplete right bundle branch block.

18. History of risk factors for Torsades de Pointes (heart failure, hypokalemia, family history of Long QT Syndrome).

19. Severe or uncontrolled cardiovascular diseases, including myocardial infarction within 3 months prior to Day 1, unstable angina pectoris, significant valvular or pericardial disease, history of ventricular tachycardia, symptomatic Congestive Heart Failure (CHF) New York Heart Association (NYHA) class III-IV, and severe uncontrolled arterial hypertension.

All exclusion criteria with the exception of criteria #5, #12, and #14 will be checked at screening visit (Visit 1). Exclusion criteria #5, #12, and #14 will be checked at Day 1 (Visit 2) only. Exclusion criteria #3, #4, #11, #13, #15, and #16 need to be re-checked at Day 1 (Visit 2).

Cycles 2 to 4:

The following exclusion criteria must be checked prior to inclusion at each repeated cycle:

1. Scheduled to receive moderately or highly emetogenic antineoplastic agent (see protocol Appendix 1) in addition to the AC regimen, from 6 hours after the start of the AC chemotherapy on Day 1 of current cycle and up to Day 1 of the next cycle.

2. Active infection or uncontrolled disease that may pose unwarranted risks in administering the study drugs to the patient.

3. Started any of the prohibited medications (see protocol Section 5.14).

4. Any vomiting, retching, or nausea (grade ≥ 1 as defined by National Cancer Institute) within 24 hours prior to the start of AC chemotherapy administration on Day 1.

5. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of AC chemotherapy administration on Day 1 or between Days 1 to 5.

6. Symptomatic primary or metastatic CNS malignancy.

7. Any illness or medical condition that, in the opinion of the investigator, may confound the results of the study or pose unwarranted risks in administering the investigational product or dexamethasone to the patient.

All exclusion criteria, with exception of criterion #4, will be checked at screening visit (Visit 1). Exclusion criterion #4 will be checked at Day 1 (Visit 2) only. Exclusion criteria #2, #3 and #5 need to be re-checked at Day 1 (Visit 2)."

Reason: To align with minor typing errors in the numbering sequence of Exclusion criteria.

Section 5. STUDY DRUG MANAGEMENT – 5.4 Dose and Administration

Amended text:

"**Test drug:** The 30-minute (+/-5 minutes) IV NEPA FDC infusion will start 30 minutes prior to the start of AC chemotherapy administration at each cycle. The IV infusion will be completed before starting chemotherapy administration.

To minimize the loss of investigational medicinal product (IMP) remaining in the infusion line after the end of IMP infusion, the following process is to be followed:

~~*3*~~*1.* At the end of the 30 +/-5 min IMP or placebo infusion, the infusion line drip chamber is to be empty.

~~*3*~~*2.* The Investigator or designated responsible person will ensure completeness of IV infusion administration by rinsing the infusion line with 20 to 30 ml sterile 5% glucose solution or sterile 0.9% saline solution. Calcium or magnesium containing solutions (e.g., Lactated Ringer solution, etc) are not allowed. The infusion line rinsing process is to be performed immediately after the end of IMP or placebo infusion and is to be completed before to start the AC chemotherapy administration."

Now reads:

"**Test drug:** The 30-minute (+/-5 minutes) IV NEPA FDC infusion will start 30 minutes prior to the start of AC chemotherapy administration at each cycle. The IV infusion will be completed before starting chemotherapy administration.

To minimize the loss of investigational medicinal product (IMP) remaining in the infusion line after the end of IMP infusion, the following process is to be followed:

1. At the end of the 30 +/-5 min IMP or placebo infusion, the infusion line drip chamber is to be empty.

2. The Investigator or designated responsible person will ensure completeness of IV infusion administration by rinsing the infusion line with 20 to 30 ml sterile 5% glucose solution or sterile 0.9% saline solution. Calcium or magnesium containing solutions (e.g., Lactated Ringer solution, etc) are not allowed. The infusion line rinsing process is to be performed immediately after the end of IMP or placebo infusion and is to be completed before to start the AC chemotherapy administration."

Reason: To align with minor typing errors in the numbering sequence.

5.9 Administration of Study Treatment

Amended text:

Administration process and relevant times:

One (1) capsule of blinded study drug (either of netupitant/palonosetron combination or matching placebo) is to be taken *with a glass of non carbonated water* 60 minutes prior to the scheduled start of AC chemotherapy administration on Day 1.

Now reads:

Administration process and relevant times:

One (1) capsule of blinded study drug (either of netupitant/palonosetron combination or matching placebo) is to be taken *with a glass of non carbonated water* 60 minutes prior to the scheduled start of AC chemotherapy administration on Day 1.

Reason: To add details about study drug administration.

Section 6. STUDY CONDUCT 6.4 Premature Discontinuation

Amended text:

"Patients may discontinue the study at any time for any of the following reasons:

~~*33.*~~ *1.* An AE occurs that, in the opinion of the Investigator, makes it unsafe for the patient to continue in the study.

~~*34.*~~ *2.* The patient is lost to follow-up.

~~*35.*~~ *3.* The patient dies.

~~*36.*~~ *4.* The patient withdraws consent.

~~*37.*~~ *5.* The Investigator, for any reason, terminates his/her participation in the study, or terminates the study for that patient; or the attending physician requests that the patient be withdrawn for any medical reason.

~~*38.*~~ *6.* The Sponsor or the Regulatory Authorities or the Ethics Committee(s), for any reason, terminates the entire study, or terminates the study for this trial site or this particular patient."

Now reads:

"Patients may discontinue the study at any time for any of the following reasons:

1. An AE occurs that, in the opinion of the Investigator, makes it unsafe for the patient to continue in the study.
2. The patient is lost to follow-up.
3. The patient dies.
4. The patient withdraws consent.

5. The Investigator, for any reason, terminates his/her participation in the study, or terminates the study for that patient; or the attending physician requests that the patient be withdrawn for any medical reason.
6. The Sponsor or the Regulatory Authorities or the Ethics Committee(s), for any reason, terminates the entire study, or terminates the study for this trial site or this particular patient."

Reason: To align with minor typing errors in the numbering sequence.