PROTOCOL NEPA-17-05

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

Statistical Analysis Plan

Prepared for:
Helsinn Healthcare SA

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Revision History

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LIST OF ABBREVIATIONS

5-HT_3	5-hydroxytryptamine type 3
AC	Anthracycline-Cyclophosphamide
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BDRM	Blinded Data Review Meeting
CI	Confidence Interval
CINV	Chemotherapy-Induced Nausea and Vomiting
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
ED	Emergency Department
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
GGT	Gamma-Glutamyl Transferase
HEC	Highly Emetogenic Chemotherapy
HEOR	Health Economics Outcome Research
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IV	Intravenous
IWRS	Interactive Web-Based Response System
LOCF	Last Observation Carried Forward

LOS	Length of Stay
MEC	Moderately Emetogenic Chemotherapy
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
N	Number of patients
NCCN	National Comprehensive Cancer Network
NCS	Not Clinically Significant
NEPA	Netupitant and Palonosetron
NIDL	No Impact on Daily Life
NK_1	Neurokinin-1
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
US	United States
VAS	Visual Analog Scale
WHODD	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment

1 INTRODUCTION

This statistical analysis plan (SAP) describes the analysis variables and statistical procedures that will be used to analyze and report the results from Protocol NEPA-17-05 (v3.1), dated 30 NOV 2017. This SAP will be finalized prior to breaking the blind. The formats for the tables and listings described in this SAP are provided in a companion document. EMB Statistical Solutions will have responsibility for performing these analyses.

The following documents were reviewed in preparation of this SAP:

- Study Protocol NEPA-17-05 v3.1, issued on 30 NOV 2017,
- electronic Case Report Form (eCRF) NEPA-17-05 v16.0, issued 23 OCT 2018.

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline, entitled "Guidance for Industry: Structure and Content of Clinical Study Reports".

The primary goal of this study is to characterize the safety profile of the test drug. No formal statistical comparisons are planned with the control group. All results will be interpreted in a descriptive manner only.

The analysis for Health Economics Outcome Research (HEOR) data will be addressed in a separate document, which includes data for hospitalization information, lost work time and productivity assessed by the Work Productivity and Activity Impairment (WPAI) Questionnaire, and disruptions in initiation and dosing of intended next cycle of chemotherapy.

2 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 patients 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 United States (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 MEC.

The oral palonosetron formulation (0.50 mg capsule) is approved in the US (August 2008) and in the European Union (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 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) [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, in combination with dexamethasone, in adults 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 the former IV netupitant formulations [6].

An IV formulation of fosnetupitant/palonosetron, IV NEPA FDC, was developed [8]. The fosnetupitant chloride hydrochloride 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.

In the US, IV NEPA FDC (Akynzeo®) was approved in April 2018, in combination with dexamethasone, in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of HEC [10].

The 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 completion of 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.

3 STUDY OBJECTIVES

3.1 Primary Objective

To evaluate the safety and tolerability of a single IV dose of fosnetupitant/palonosetron (260 mg/0.25 mg) combination (IV NEPA FDC) 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.

3.2 Secondary Objective

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.

3.3 Exploratory Objective

To evaluate the impact on economics and resource utilization through collection of HEOR parameters in initial and repeated cycles of AC chemotherapy.

4 TREATMENT PLAN AND STUDY DESIGN

4.1 General Design

This is a 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 (IV NEPA FDC) versus oral netupitant/palonosetron (300 mg/0.5 mg) combination (oral NEPA FDC); 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. 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. Oral NEPA FDC (or matching placebo) is to be administered 60 minutes prior to the start of AC chemotherapy administration. IV NEPA FDC (or matching placebo) 30-minute infusion is to begin 30 minutes prior to the start of AC chemotherapy administration, and is to be completed before starting AC chemotherapy. Dexamethasone (3 tablets of 4 mg, 12 mg total) is to be given immediately before the start of the IV NEPA FDC (or matching placebo) infusion.

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 and AC chemotherapy, patients will enter an efficacy evaluation period of 120 hours and then return to the clinical site on Day 6 (+ 2 days) 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, 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 (Visit 1) and the study drug administration visit (Visit 2) can be performed on the same day. The screening visit of a subsequent cycle can also coincide with the follow-up visit (Visit 4) 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, the 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 AC 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 with a 21-day 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 (400th) patient is randomized, in order to permit patients already

screened for a subsequent study cycle to have study drug administered. 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.

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 study 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.

See Appendix A for a flow chart of assessments to be collected, activities to be performed, and relevant study visits.

4.2 Blinding and Randomization

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

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 a statistician at EMB Statistical Solutions not assigned to the study team, who will keep the study team blinded to the codes and all other information (e.g., the seed) that could break the blind of the study. A master randomization list copy will be filed securely by EMB and the Sponsor in a manner that ensures that blindness is properly maintained throughout the trial. The biostatistician involved in the creation of the 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 an Interactive Web Response System (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.

4.3 Determination of Sample Size

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 in the interpretation of any unexpected safety finding in the test group.

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1 Changes in the Conduct of the Study

There have been the following versions of the protocol: v1.0, v1.1, v1.2, v2.0, v3.0, and v3.1. No patients were enrolled prior to Protocol v3.1 dated 30 Nov 2017, and this first SAP version is based on Protocol v3.1.

5.2 Changes from the Analyses Planned in the Protocol

This analysis plan details analyses to be conducted for the study. Some of the analyses detailed here may be more explicit than those stated in the protocol. In case of differences, this SAP provides details of the changes and supersedes the statistical sections in the protocol.

6 BASELINE, EFFICACY, AND SAFETY ASSESSMENTS

6.1 Schedule of Evaluations

The assessments to be conducted at each scheduled visit are displayed in Appendix A.

6.2 Definitions/Terminology

- **Baseline**: the last non-missing evaluation which was collected prior to the first study drug (oral and IV NEPA FDC or matching placebo) intake in Cycle 1. Some by-cycle change summaries are also planned using the pre-dose assessment from each cycle (i.e., last non-missing evaluation which was collected prior to study drug intake in that cycle) in addition to a change summary using Baseline; such cases will be indicated.

- **Disposition:**
  - Completed study patient: completes Visit 4 (either as on-site visit or telephone contact) of Cycle 4.
  - Completed cycle, not continuing patient: completes Visit 4 (either as on-site visit or telephone contact) of any cycle before Cycle 4 without continuing in the subsequent cycle.
  - Premature study discontinuation: Study termination at a different time point other than Visit 4 of any cycle (including screening visit for one of the repeated cycles).

- **Medications**:
  - Prior medications: all medications taken prior to the date of first study drug (oral and IV NEPA FDC or matching placebo) intake in Cycle 1.
  - Concomitant medications: all medications taken on or after the day of first study drug (oral and IV NEPA FDC or matching placebo) intake in Cycle 1. Note that a medication taken within 14 days prior to Day 1 of Cycle 1 and ongoing at the time of the start of study treatment will be considered as both a prior and concomitant medication.
  - Compliant patient: takes all study drugs (oral NEPA FDC/Placebo, IV NEPA FDC/Placebo, and dexamethasone). Defined overall and for each cycle.

- **Chemotherapies**:
  - Concomitant chemotherapies: chemotherapies taken any time in the interval Day 1-5 of each cycle.

- **Efficacy**:
  - Time 0: start time of the AC chemotherapy administration on Day 1 of each cycle.
  - Phases: acute, delayed, and overall are time intervals 0 to 24 hours, > 24 to 120 hours and 0 to 120 hours after the start of the AC chemotherapy administration, respectively.
  - Emetic episode: 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.
  - Rescue medication: 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. Permitted on an as-needed basis.
  - Complete response (CR): no emetic episodes (vomit or retch) and no use of rescue medication during applicable phase.
  - Nausea severity: defined using maximum nausea intensity on a 100-mm horizontal visual analog scale (VAS). The left end of the scale (0 mm) is labeled as ‘no nausea’, and the right end of the scale (100 mm) is labeled as ‘nausea as bad as it could be’.
  - No nausea: maximum nausea intensity on a 100-mm VAS of < 5 mm during applicable phase.
  - No significant nausea: maximum nausea intensity on a 100-mm VAS of < 25 mm during applicable phase.
  - No impact on daily life (NIDL): a 5-day Functional Living Index-Emesis (FLIE) questionnaire score greater than 108 points, 54 points, and 6 points for the total score, domain score, and single item score, respectively [11].

- **Safety**:
  - Pre-treatment adverse events (AEs): AEs that start prior to the first study drug (oral and IV NEPA FDC or matching placebo) administration on Day 1 of Cycle 1.
  - Treatment-emergent adverse events (TEAEs): AEs that start or worsen in severity after the first study drug (oral and IV NEPA FDC or matching placebo) administration on Day 1 of Cycle 1 until Visit 4 of the last study cycle.
  - Drug-related AEs: AEs with study drug (oral and IV NEPA FDC or matching placebo) relationship classified by investigator as definitely, probably, possibly, unassessable, or missing.

6.3 Efficacy Endpoints

Efficacy is the secondary objective of the study and will be assessed by the following efficacy endpoints:

- Proportion of patients with CR during the acute, delayed, and overall phases;
- Proportion of patients with no emetic episodes during the acute, delayed, and overall phases;
- Proportion of patients with no rescue medication during the acute, delayed, and overall phases;
- Proportion of patients with no nausea during the acute, delayed, and overall phases;
- Proportion of patients with no significant nausea during the acute, delayed, and overall phases;
- Severity of nausea in the acute, delayed, and overall phases;
- Proportion of patients with NIDL activities in the overall phase of Cycle 1 and 2, only as assessed by the FLIE questionnaire;
- Domain (nausea and vomiting) FLIE scores and the total FLIE score in the overall phase of Cycle 1 and 2 only.

Note: since the nausea VAS is assessed daily, for no nausea, no significant nausea, and severity of 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 the maximum value for Day 1 to 5 for the overall phase).

Note: The manual for the FLIE questionnaire indicates that the scale anchors are in the opposite direction on Items 3, 6, 11, 15, and 18 compared to the other items, and so a respondent may answer one or more items incorrectly as a result. A response on one of these items can be considered invalid if the item score is ± 50 mm or more from the mean score of the items from the same domain (excluding items 3, 6, 11, 15, and 18). In these cases, as is recommended by the manual, the item, domain, and total scores will be calculated and reported "as is" (i.e., using

the value marked by the respondent). If the percentage of invalid scores is ≥10%, then a sensitivity analysis will be performed to assess the impact of these errors by setting the invalid item(s) to missing before calculating the domain and total scores.

6.4 Safety Assessments

Safety is the primary objective of the study and will be assessed primarily by means of:

- TEAEs.

Additionally, the assessment of safety will be based on:

- clinical laboratory values (hematology and blood chemistry),
- vital signs, and
- physical examinations.

Additional key details for safety assessments are provided in the sections below.

6.4.1 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.

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 AE 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.

The Investigator will classify AEs based on their severity (Grades 1-5) and relationship to Investigational Medicinal Product (IMP) and dexamethasone (definitely related, probably related, possibly related, unlikely related, not related/none, and unassessable). 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) [12].

6.4.2 Clinical Laboratory Evaluations

At the screening visit for each cycle, the Investigator will be responsible for assessing a patient's eligibility to receive AC chemotherapy, including the assessment of laboratory parameters. The following laboratory parameters will be assessed at Visit 1 (Screening) and Visit 3 (Day 6 + 2 days) of each cycle using local laboratories:

- Hematology: hemoglobin, erythrocytes, leukocytes, and 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).

Upon receipt and after review, the Investigator must sign and date each local laboratory report and document in the relevant eCRF form if the parameter is below, within, or above normal ranges and, in case of abnormal values, if they are clinically significant.

Laboratory values, units, and ranges will not be entered in the eCRF nor provided to EMB via an external data transfer.

6.4.3 Vital Signs

Vital signs assessments will include pulse rate, systolic and diastolic blood pressure (at Visit 1, Visit 2 pre-dose and Visit 3 of each cycle); height (Visit 2 of Cycle 1 only); and body weight, body surface area, and body mass index (Visit 2 [Day 1 visit] of each cycle, at pre-dose). Pulse rate and systolic and diastolic blood pressure will be measured after the patient has been resting in the semi-supine position for at least 5 minutes.

6.4.4 Physical Examinations

A complete physical examination will be performed at Visit 1 (Screening) and 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. Full results for each test will only be recorded in the eCRF for Cycle 1 Visit 1 (Screening).

7 STATISTICAL METHODS

7.1 General Methodology

Data will be summarized using descriptive statistics (number of patients [N], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and using frequency and percentage for discrete and categorical variables.

The summaries will be presented by the two treatment arms the patients are randomized to: (1) IV NEPA FDC or (2) Oral NEPA FDC.

Patient listings of data from the eCRFs as well as derived variables will be provided. An indication of specific listings for each data type will not be indicated in the text of subsequent sections. The specific listings planned, along with their formats, are provided in a companion shell document.

Procedures, Adverse Events, and Medical Diseases (including current cancer history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. The verbatim term will be mapped to System Organ Class (SOC), High Level Group Term, High Level Term, Preferred Term (PT), and Low Level Term.

Prior and Concomitant Medications (including rescue medications recorded in patient diary and chemotherapies) will be coded using the World Health Organization Drug Dictionary (WHODD) March 2018 enhanced version. Medications will be coded to generic name and Anatomical Therapeutic Chemical (ATC) classification of ingredients (i.e., therapeutic class).

7.2 Interim Analyses

No formal interim analyses are 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.

7.3 Final Analyses and Reporting

A blinded data review meeting (BDRM) will be held prior to database lock. This SAP should be approved before study unblinding.

Tables and Listings will be made available following database lock and unblinding and prior to completion of the final Clinical Study Report (CSR).

Any post-hoc analyses completed to support planned study analyses which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses will also be clearly identified in the text of the CSR.

7.4 Handling of Missing Data

No imputations will be performed on missing demographics, background, or safety data and only observed cases will be reported unless otherwise noted in this SAP. See Section 7.8.5 below for the handling of missing start dates to determine prior and concomitant medications. See Section 7.11.2 below for the handling of missing AE start dates to determine treatment-emergent status, missing AE severity, and missing AE relationship to study treatment.

For efficacy analyses, the procedures for handling missing data are described below and will be applied to the Full Analysis Set (FAS).

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

The following bullets provide a description for procedures related to CR determination:

- For efficacy analyses, a patient will be considered as having CR only if there is documented evidence of both no occurrence of emetic episodes and no rescue medication intake. Any patient who does not provide data about occurrence of emetic episodes and rescue medication intake is to be considered as a 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 be applied to emetic episodes and rescue medication intake.

- Emetic episodes recorded on the patient diary that occurred outside the time window of 0-120 hours with reference to start of AC chemotherapy administration will be kept but will not be used for the statistical analysis of CR. Vomiting and retching episodes will be combined first, then episodes outside of the 0-120 hour window will be dropped (i.e., drop episodes starting before AC chemotherapy administration or starting after 120 hours). If all episodes recorded on the patient diary actually occurred outside the 0-120 hour window, the answer to the general question about emetic episodes should be consistently considered "No". A similar approach will be applied to rescue medication intake.

- Since there might be cases where emetic episodes and rescue medications intake in the 0-120 hours from start of AC chemotherapy are recorded in the eCRF Adverse Events and Prior and Concomitant Medications forms only (and not, as it should, 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. In this respect, AEs with PTs “Vomiting” and “Retching” will be considered. The start and stop dates of the AE episode will be used to determine AEs for the 0-120 hour time interval. If no start and stop times are recorded for the AEs, only those events that clearly occurred in the 0-120 hour time interval will be considered for efficacy analysis, i.e., if an AE stops on the first day of the 0-120 hour period or starts on the last day of the 0-120 hour period, then this AE episode will not be taken into consideration for efficacy analysis since assumed these cases were correctly recorded by the investigator. For the AEs that clearly occurred in the 0-120 hour time interval, if there is evidence that they were actually due to lack of efficacy, they will be taken into account for efficacy but not for safety analyses.

- In cases where an emetic episode has been recorded twice, once as a clinical event in the diary and once as an adverse event in the AE form, but with exactly the same start and end date and time values, it will be considered for both the efficacy and safety analyses.

- For concomitant medications, drugs with an indication for treatment of nausea, vomit, CINV, emesis, retching, or similar will be considered. Start and stop dates will be used to determine rescue medications taken in the 0-120 hour time interval. If no start and/or stop time are recorded, only the intakes that clearly occurred in the 0-120 hour time interval will be considered for efficacy analysis. A time value of “00:00” will be imputed for missing times for the determination of phase for such cases.

- All TEAEs and concomitant medications meeting any of the above criteria will be identified and a listing will be created for review at the BDRM. Decisions on how to deal with these cases will be fully documented and appended to the BDRM minutes, which will be finalized before database lock. Records from AEs and the concomitant medications forms used for the CR determination will be flagged in the efficacy listings for emetic episodes and rescue medication intake.

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 (region and age class). 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 of each domain, expressed in mm (after reversing items with the scale anchors in the opposite direction), 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 as follows:

Domain score (in FLIE points) = (Domain score (in mm) × 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 FLIE single item will not be replaced. A missing entire FLIE 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 and same region. The total FLIE score will be then calculated from the complete data after imputation of missing data.

7.5 Analysis Populations

The study populations are defined as follows:

- **Full Analysis Set (FAS) -** 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. The FAS population will be used for demography, other baseline characteristics, and all descriptive efficacy analyses.

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

If any patients receive incorrectly administered kits that result in different active treatments received by cycle, they will be handled as follows for tables in the Safety population:

- Tables for demography, other baseline characteristics, prior and concomitant medical diseases/medications/radiologic treatments/procedures, and overall study drug compliance/exposure will use actual treatment received from Cycle 1.
- Tables for study drug compliance/exposure, adverse events, laboratory values, and vital signs that summarize data by cycle will use actual treatment received from the applicable cycle.

7.6 Protocol Deviations

A list of potential deviations is included in the Protocol Deviations Document. Since the main study objective is the assessment of the safety profile of the IV study drug combination, deviations will be defined but they will not determine the exclusion of patients from any populations (i.e., no Per-Protocol population is defined, see Section 7.5).

Deviations include, but are not limited to, inclusion/exclusion criteria not met, missing diaries, intake of non-permitted medications, and incorrect randomizations. All deviations will be reviewed and discussed case by case during the BDRM and decisions will be described in the blind data review document/minutes, which will be finalized prior to database lock. The IMP deviations requiring knowledge of active or placebo treatment receipt to determine a major versus minor grade will be assigned as major prior to database lock, which then may be downgraded to minor after unblinding if applicable.

The number and percentage of patients with deviations will be tabulated by deviation, by treatment group, and overall for all randomized patients.

7.7 Patient Disposition

The number of patients screened, failed screening, randomized, completed study, completed cycle/not continuing, and with premature study discontinuation will be summarized descriptively by treatment group and overall. The primary reasons for premature study discontinuation will also be presented (including patients defined as “completed a cycle, not continuing”).

For each cycle, the number of patients scheduled for treatment (i.e., had a study drug kit assigned for that cycle); treated; completed Visit 4 of cycle, continuing; completed cycle, not continuing; and discontinued during that cycle will be also displayed.

The number of patients included in the Safety and FAS populations and reasons for exclusion from those populations will also be tabulated by treatment group and overall for randomized patients.

7.8 Analysis of Demographics, Other Baseline Characteristics and Conditions

7.8.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics (age, age class, region, gender, fertility status, race, ethnicity, height, weight, body mass index, body surface area, Eastern Cooperative Oncology

Group Performance Status [ECOG PS], tobacco consumption, number of cigarettes/cigars per day, alcohol consumption, and illicit drug use) will be summarized descriptively by treatment group and overall for the Safety and FAS populations. These characteristics will be also summarized by stratification factors, i.e., by age class and region.

A separate table for the Safety population will descriptively summarize current cancer diagnosis (location, histological/pathological type, time since histological diagnosis [days], extent at study entry, and site of metastasis) by treatment group and overall. Current cancer history also will be summarized by MedDRA High Level Group Term and Preferred Term and by treatment arm and overall.

7.8.2 Anthracycline-Cyclophosphamide and Concomitant Chemotherapies

A separate table for each cycle will descriptively summarize the number and percentage of patients by AC regimens in the FAS population, which will display the combination of the chemotherapeutic drugs administered by concatenating the generic medication names received by a patient. E.g., CYCLOPHOSPHAMIDE + DOXORUBICIN, CYCLOPHOSPHAMIDE + EPIRUBICIN, etc.

Summary statistics for dose (actual dose on Day 1 expressed in mg and as mg/m^2) for each of the components of the AC regimen will be presented by cycle as well.

Number and percentage of patients taking concomitant chemotherapies agents (chemotherapies taken any time in the interval Day 1-5) by time of intake with respect to AC regimen (i.e., Day 1 only or Days 1-5) will be presented for each cycle. Concomitant chemotherapies received in addition to the AC regimen will be presented in a frequency table by WHODD generic medication name for each cycle.

A similar presentation will be displayed for patients taking chemotherapies with a start date > 120 hours after AC chemotherapy administration at each cycle.

7.8.3 Medical Diseases

Medical diseases will be tabulated by MedDRA SOC and PT for the Safety population for each treatment group and overall, separately for prior and for concomitant diseases. Medical disease terms with ongoing checked 'No' will be considered as prior diseases, and with ongoing checked 'Yes' as concomitant diseases.

7.8.4 Baseline Physical Examination

The Cycle 1 Visit 1 (Screening) physical examination findings (normal/abnormal/not done) will be summarized descriptively for the Safety population by treatment group.

7.8.5 Prior and Concomitant Medications/Radiotherapies

Prior medications and concomitant medications (excluding rescue medications) will be summarized separately by treatment group and overall for the Safety population by displaying frequency counts and percentages by WHODD ATC Class Level 4 (if Level 4 is not available,

will use the highest class available) and WHODD generic name. A patient will be counted only once per therapeutic class or generic name.

Since prior and concomitant radiologic treatment verbatim terms are not planned to be coded, only the number of patients with at least one prior and with at least one concomitant radiologic treatment will be presented by treatment group and overall for the Safety population. Treatment details for individual patients will be listed.

The following approach will be taken to determine whether a medication is to be considered prior or concomitant, where an incomplete start date exists:

1) When the month and year are known but the day is missing: If the first study drug administration is during or prior to that month, then the medication is to be considered as concomitant. If the first study drug administration is after that month, then the medication is to be considered a prior medication; in addition, if the medication is continued after the first study drug administration then it will be counted as both a prior medication and a concomitant medication.

2) When the year is known but both the day and the month are missing: If the first study drug administration is during or prior to that year, then the medication is to be considered as concomitant. If the first study drug administration is after that year, then the medication is to be considered a prior medication; in addition, if the medication is continued after the first study drug administration then it will be counted as both a prior medication and a concomitant medication.

7.8.6 Prior and Concomitant Procedures

Prior and concomitant diagnostic/therapeutic/surgical procedures will be summarized by MedDRA SOC and PT and by treatment arm and overall for the Safety population. Prior procedures and concomitant procedures will be presented separately.

7.8.7 Compliance

A summary of investigational study drug and dexamethasone compliance overall and by cycle will be provided by treatment group for the Safety population.

7.9 Efficacy Analysis

Analyses of efficacy endpoints will be performed using the FAS population. All results will be interpreted in a descriptive manner only.

7.9.1 Complete Response, No Emetic Episodes, No Rescue Intake, No Nausea, and No Significant Nausea

At each cycle, for each phase (acute, delayed, and overall), numbers and proportions (including two-sided 95% confidence interval [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 by treatment group. For these variables, the treatment difference

(IV-oral NEPA FDC) in response rate will be presented with a two-sided 95% CI using the Cochran-Mantel-Haenszel (CMH) method adjusted for region and age class strata. A treatment difference two-sided 95% CI using Newcombe-Wilson's method without strata adjustment will also be presented.

In addition for Cycle 1, CR in the acute, delayed, and overall phases will be summarized for each treatment group by region strata and separately by age group strata. Numbers and proportions (including two-sided 95% CI using Wilson score method) of patients with CR will be provided, as well as treatment difference with a two-sided 95% CI using Newcombe-Wilson's method without strata adjustment.

Overall phase CR will be summarized by region and investigative site for Cycle 1 with numbers and proportions.

In addition, rescue medications for individual cycles will be summarized by treatment group and overall for the FAS population by displaying frequency counts and percentages by WHODD ATC Class Level 4 (if Level 4 is not available, will use the highest available) and WHODD generic name. A patient will be counted only once per therapeutic class or generic name.

7.9.2 Severity of Nausea

For each cycle, the maximum severity of nausea based on the 100-mm VAS in the acute, delayed and overall phases will be descriptively summarized by treatment group. The difference of means (IV-oral NEPA FDC) will be presented with a two-sided 95% CI, using the t-test method without strata adjustment.

7.9.3 Functional Living Index-Emesis Scores and No Impact on Daily Life

In Cycle 1 and Cycle 2 only, the number and proportion (including two-sided 95% CI using Wilson score method) of patients with NIDL based on FLIE scores (overall, by domain, and by individual item) will be summarized by treatment group. Differences between treatment groups for total FLIE score and domain scores (nausea and vomiting) will be presented with two-sided 95% CIs using the CMH method adjusted for region and age class strata and also using Newcombe-Wilson's method without strata adjustment.

For Cycle 1 and Cycle 2, the nausea and vomiting domain FLIE scores and the total score will be descriptively summarized by treatment group. The difference of means (IV-oral NEPA FDC) will be presented with a two-sided 95% CI, using the t-test method without strata adjustment.

7.10 Subgroup Analyses

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 so to minimize possible imbalance between groups.

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

7.11 Safety Analysis

Summaries of safety data will be based on the Safety population. No formal tests will be performed to compare treatment groups.

7.11.1 Extent of Exposure

A table with exposure to study drug and dexamethasone for the Safety population for each cycle will summarize by treatment group whether or not patients received the Oral NEPA FDC/Placebo capsule, oral dexamethasone (12 mg, 8 mg, or 4 mg total), and IV NEPA FDC/Placebo infusion. In addition, the location of the IV NEPA FDC/Placebo infusion (left arm, right arm, central access, or other), whether or not the infusion was interrupted, the cumulative infusion volume administered (mL), and whether or not the infusion line was rinsed will be summarized.

A table with exposure to study drug and dexamethasone for the Safety population for the entire study will summarize by treatment group the total number of Oral NEPA FDC/Placebo capsules and IV NEPA FDC/Placebo infusions received, the total cumulative volume of IV NEPA FDC/Placebo solution administered, and the total number of oral dexamethasone tablets received.

7.11.2 Adverse Events

A conservative approach will be used to handle incomplete dates for AEs. As a general principle, AEs with missing or incomplete date of onset will be assumed to be treatment emergent, unless there is clear evidence (through comparison of partial date with date of first study drug administration) that the AE started prior to the first dose of study treatment.

If the onset date is unknown but the stop date is available and is before first study drug administration, then the AE will not be considered as a TEAE.

The rules for handling incomplete AE onset dates will be as follows:

1) When the month and year are known and the day is missing: If first study drug administration is during or prior to that month, then the AE is to be considered treatment emergent; if first study drug administration is after that month, then the AE is not to be considered as treatment emergent.

2) When the year is known and both the day and the month are missing: If the first study drug administration is during or prior to that year, then the AE is considered to be treatment emergent; if first study drug administration is after that year, then the AE is not to be considered treatment emergent.

Date imputation rules will be specified in the study analysis dataset specifications with further details.

AEs with missing severity or relationship to study treatment will have the assessment considered as "unknown" (missing) for AE listings. For AE tables, events with missing severity will be

treated as Grade 3 (severe) and with missing or unassessable relationship to study treatment will be considered as related.

TEAEs will be summarized by SOC and PT, sorted alphabetically by SOC and in decreasing overall frequency across both treatment groups by PT, unless specified otherwise. For patient counts, a patient will only be counted once per SOC and once per PT in cases where multiple events are reported for a patient within SOC or PT. For event counts, patients with multiple events in a category will be counted for each event.

Patient counts and percentages will be presented for the following summaries by treatment group:

1) Overall summary of TEAEs for all cycles and separately for Cycle 1: patients with at least one TEAE, patients with at least one TEAE classified as drug-related, serious, drug-related serious, with fatal outcome, drug-related with fatal outcome, severe (Grade ≥ 3), drug-related severe, leading to premature study discontinuation, and drug-related leading to premature study discontinuation. The total number of events in each category will also be provided in the same table.

2) TEAEs by SOC and PT for all cycles and separately for Cycle 1. The total number of events in each category will also be provided in the same table.

3) TEAEs by SOC, PT, and maximum severity (Grade 1 through 5) for all cycles and separately for Cycle 1.

4) Severe (Grade ≥ 3) TEAEs by SOC and PT for all cycles and separately for Cycle 1.

5) TEAEs by SOC, PT, and strongest relationship to study drug for all cycles and separately for Cycle 1. Categories displayed will be definitely, probably, possibly, unlikely, none, and unassessable/missing. Similar tables for relationship to dexamethasone and for relationship to study drug or dexamethasone will be provided.

6) Drug-related TEAEs by SOC and PT for all cycles and separately for Cycle 1.

7) TEAEs occurring in at least 5% of patients in any treatment group by SOC and PT for all cycles and separately for Cycle 1.

8) Drug-related TEAEs occurring in at least 2% of patients in any treatment group by SOC and PT for all cycles and separately for Cycle 1.

9) TEAEs of special interest, i.e., "infusion site TEAEs" by PT for all cycles and by cycle. An initial list of terms to be considered for infusion site AEs includes: "Pain, Erythema, Swelling, Hives, Extravasation, Deep vein thrombosis, Superficial thrombosis, Phlebitis/Thrombophlebitis, Vein discoloration, Venous engorgement, Venous hardening/induration, Local scarring, Itching sensation, and Heat sensation" [13, 14]. Since some terms are general (e.g., pain, erythema), location will be needed to determine if the AE is to be categorized as an "infusion site AE" or not. Other terms may be identified by

clinicians during the study and prior to database lock. The final list of PTs will be reviewed and approved at the BDRM.

10) Drug-related infusion site TEAEs by PT for all cycles and by cycle.

11) Serious TEAEs by SOC and PT for all cycles and separately for Cycle 1.

12) Drug-related serious TEAEs by SOC and PT for all cycles and separately for Cycle 1.

13) TEAEs leading to premature study discontinuation by SOC and PT for all cycles and separately for Cycle 1.

14) Drug-related TEAEs leading to premature study discontinuation by SOC and PT for all cycles and separately for Cycle 1.

15) TEAEs with fatal outcome by SOC and PT for all cycles.

16) Drug-related TEAEs with fatal outcome by SOC and PT for all cycles.

For the summary of TEAEs by severity, if a patient has multiple events occurring in the same SOC or same PT, then the event with the highest severity will be counted. Similarly for tabulations by relationship to study drug, a patient will be counted once in the category with strongest relationship to study drug.

Separate listings will be provided for pre-treatment AEs, all TEAEs (including onset day relative to first and last study drug intake), all TEAEs with fatal outcome, all serious TEAEs, and all TEAEs leading to premature study discontinuation.
In addition a specific listing for "infusion site TEAEs" will be created, including details for location of AC chemotherapy and IV NEPA FDC/placebo infusion.

7.11.3 Clinical Laboratory Evaluations

As mentioned in Section 6.4.2, each abnormal laboratory value, relative to local normal laboratory range, will be assessed as clinically significant (CS) or not clinically significant (NCS) by the investigator.

Proportion of laboratory values low (low CS, low NCS), normal, and high (high NCS, high CS) will be presented by frequency table for each time point and treatment group.

In addition, shift tables (low, normal, high) will be presented by treatment group and cycle comparing Visit 3 (Day 6) value to Baseline and, for Cycle 2 onwards, comparing Visit 1 (Screening) also to the Baseline assessment. Shift tables comparing Visit 3 (Day 6) value to Visit 1 (Screening) within cycle will also be produced.

For patients who have a clinically significant abnormal laboratory value, a listing will display individual assessments for that analyte across all visits.

7.11.4 Vital Signs and Weight

Vital signs (pulse rate, systolic, and diastolic blood pressure) and weight based measures will be summarized by treatment group and time point using descriptive statistics for absolute values and change from Baseline. In addition for Cycle 2 vital signs onwards, change from pre-dose assessment of each cycle will be summarized.

8 REPORTING CONVENTIONS

All analyses will be performed using Version 9.4 or later of SAS® software. All summary tables and data listings will be prepared utilizing SAS software. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data.

Unless otherwise specified, frequency tabulations will be presented by number and percentage, where the percentage is presented in parentheses to one decimal place. Frequency and percentage values of 0 will be presented as ‘0’ without ‘0.0%’.

All summary tables will indicate the analysis population sample size (i.e., number of patients).

All listings will be sorted by treatment group, patient number, assessment dates, and/or time point.

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APPENDIX A: FLOW CHART

Study Phase	*Study Cycle (Cycle 1 / Repeated Cycles)*			
Procedure/assessment	Screening Day -14 to 1 (Cycle 1 only) / Day -7 to 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), the 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 of the protocol 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 has 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 hematology 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 until end of the study (completion/discontinuation), as a minimum. If the patient exits 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 Protocol Section 8.1.3.1.