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TITLE: A Phase II Clinical Trial of NEPA (Netupitant/Palonosetron) for Prevention of Chemotherapy Induced Nausea and Vomiting (CINV) in Patient Receiving the BEAM Conditioning Regimen Prior to Hematopoietic Cell Transplantation (HSCT)

Coordinating Center: Oregon Health and Science University Hospital and Clinics

Principal Investigator: Joseph Bubalo PharmD, BCPS, BCOP
Pharmacy Services, CR 9-4
3181 SW Sam Jackson Park Road
Portland, OR 97239
503-494-8007
Fax 503-494-5094
bubaloj@ohsu.edu

Co-Investigators: Richard T. Maziarz, MD
Andy Chen, MD, PhD
Sarah Nagle, MD

Biostatistician: Jeong Youn Lim, PhD
Biostatistics Shared Resource, CR-145
Knight Cancer Institute
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, OR 97239
503-418-1555
limje@ohsu.edu

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SCHEMA

Phase II Clinical Trial of NEPA (Netupitant/Palonosetron) for Prevention of Chemotherapy Induced Nausea and Vomiting (CINV) in Patient Receiving the BEAM Conditioning Regimen Prior to Hematopoietic Cell Transplantation (HSCT)

Staged Study: Stage I

Enroll 13 Patients receiving BEAM preparative chemotherapy for HSCT (chemotherapy Days 1-6: highly emetogenic on Days 1 & 6 and moderately emetogenic Days 2-5)

↓

Study drug (NEPA) Days 1, 3, and 6
with Dexamethasone (Days 1-6)
and chemotherapy Days 1-6

↓

Monitor patient nausea and emesis with self-reported assessments and hospital chart review (Episodes of emesis, Need for rescue therapy)

↓

If 4 or more complete responses (CR) then proceed to Stage II
If 3 or fewer CRs then declare futility.

↓

Stage II

Enroll 30 additional patients receiving BEAM preparative chemotherapy for HSCT

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Repeat Study drug (NEPA) Days 1, 3, and 6
with Dexamethasone (Days 1-6)
and chemotherapy Days 1-6

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Monitor patient nausea and emesis with self-reported diaries and hospital chart review (Episodes of emesis, Need for rescue therapy)

Contents

1.0 OBJECTIVES

1.1 Primary Objective

To assess the efficacy of NEPA to prevent nausea and vomiting both during and after a highly emetogenic (BEAM) conditioning regimen for hematopoietic stem cell transplantation (HSCT). The efficacy is measured by Complete Response (CR) defined as no emesis and no rescue therapy for hours 0-264 (6 days of chemotherapy and 5 days post-chemotherapy).

1.2 Secondary Objectives

To differentiate response to NEPA over different phases of chemotherapy-induced nausea. Specifically, CR is assessed for hours 0-144 (Acute phase) and hours 145-264 (delayed phase), and Complete Protection (CP) defined as CR plus no nausea is assessed for hours 0-144, 145-264, and the whole period.

2.0 BACKGROUND

2.1 Chemotherapy-induced nausea and vomiting (CINV)

Abstract

The management of chemotherapy-induced nausea and vomiting (CINV) during preparative regimens for Hematopoietic Stem Cell Transplant (HSCT) continues to be a poorly studied area and an unmet patient need. Still unaddressed in the most recent evidence based guidelines such as American Society of Clinical Oncology (ASCO) and Multinational Association Of Supportive Care In Cancer (MASCC), patients undergoing high dose antineoplastics as they prepare for autologous or allogeneic stem cell rescues have a high risk for emesis. Preparative regimens are generally multiple days of high dose chemotherapy, which result in the risk for a combination of acute and delayed emesis. NEPA with the combination of neurokinin 1 antagonist and serotonin antagonist represents a unique product to address both types of CINV in a single agent. Thus we propose to use it to prevent CINV in patients receiving the BEAM (carmustine, etoposide, cytarabine, and melphalan) preparative regimen. This regimen is a 6-day therapy course with high dose (and highly emetogenic) chemotherapy on day 1 and 6 with lower risk chemotherapy for acute emesis on days 2 through 5. Our plan is to dose NEPA on days 1, 3, and 6 to cover the complete course of therapy and continue to monitor for 5 days after to assess for control of delayed CINV as well as acute. Given the current poor levels of control with previously available agents and scant experience with multiday dosing of NEPA we propose a phase II trial to gain baseline safety and efficacy data without a placebo arm. Advancement in management of CINV has been critical in administering highly emetogenic agents required for myeloablative conditioning regimens in HSCT. However, there remains a need for safe, effective, and reliable agents to eradicate CINV. Furthermore, delayed-onset CINV is increasingly recognized as more difficult to treat than acute-phase CINV.

NEPA is a recently approved combination antiemetic, containing fixed doses of netupitant (an NK1 receptor antagonist) and palonosetron (a 5HT3 receptor antagonist). Having pharmacologically distinct mechanisms, combined NEPA offers synergistic reduction and potential elimination of CINV. NEPA has previously been shown to be superior to palonosetron in single and multiple cycles of both highly[1] and moderately[1,2] emetogenic chemotherapy regimens.

Mechanism and Clinical Importance

From the earliest use of cytotoxic chemotherapies, nausea and vomiting have been a limiting factor in treatment. Significant advancements have been made in understanding the underlying cause of chemotherapy-induced nausea and vomiting (CINV) as well as in managing it. CINV has three distinct subtypes – acute, delayed and anticipatory. While there have been improvements in the prevention of all three areas, CINV remains problematic especially with highly emetogenic chemotherapies (HEC) and in the delayed-onset setting (occurring over 24 hours after chemotherapy administration).

Several areas of the brain and their associated neurotransmitters have been implicated in the development of nausea and vomiting. Specifically, the chemoreceptor trigger zone (CTZ) at the caudal end of the fourth ventricle in the area postrema lacks an effective blood brain barrier, permitting chemical stimuli from blood and cerebrospinal fluid (CSF) to activate the CTZ and induce the sensation of nausea and the emesis response. Four major neurotransmitter systems, the dopaminergic (D_2), histaminic (H_1), serotonergic (5-HT_3), and cholinergic (muscarinic), have been implicated in inducing this response and blockade of these receptors have been effective in managing nausea and emesis.

The subnucleus gelatinosus at the nucleus tractus solitarius (NTS), a convergence of afferent neurons from the vagal and vestibulary systems and efferents from the area postrema, has also been identified as critical for initiating emesis. In this area, the neurokinin 1 receptor agonist Substance P acts as a common chemical signal for neuronal communication.[3] Blockade with NK1 receptor antagonists has demonstrated additive antiemetic efficacy.

Delayed onset nausea and emesis have been largely associated with the activation of tachykinin family neurokinin 1 (NK_1) receptors (broadly distributed in the central and peripheral nervous systems) by substance P[4,5]. As shown in in vitro and in vivo studies, netupitant inhibits substance P mediated responses. In vitro administration of both netupitant and palonosetron demonstrated an additive internalization of the NK1 receptor.[6]

While not directly life threatening, impaired quality of life and morbidity from poorly controlled CINV continues to be a problem. Sequelae of CINV include poor adherence to chemotherapy regimens, anxiety, impaired nutrition and risk of dehydration, and mucosal damage with exacerbation of mucositis, which is already an adverse effect of many chemotherapies. Further, in a recent review of 67 studies, Sommariva et al. highlight the effect on health-related quality of life and the additional health-care cost of poorly

controlled CINV. In this study, specific costs were highly variable, but reviewed studies agreed that CINV led to increased medication expenditure and inpatient, outpatient, and emergency department visits; however, the addition of palonosetron, a 5-HT_3 receptor antagonist, reduced use of rescue medications and the further addition of aprepitant, an NK_1 receptor antagonist, provided benefit in certain populations receiving HEC.[7]

Current Therapy

Current treatment recommendations for management of CINV in highly emetic chemotherapy (HEC) are for triple therapy with an NK_1 receptor antagonist (NK_1RA), 5-HT_3 receptor antagonist (5-HT_3RA), and dexamethasone. Four 5-HT_3RAs - ondansetron, granisetron, dolasetron, and palonosetron are available as antiemetics in the United States. Palonosetron has demonstrated superiority over the other 5-HT_3RAs because it helps to control delayed CINV in addition to acute CINV, whereas the other 5-HT_3RAs (ondansetron, granisetron, dolasetron) are primarily active only in acute CINV. Further, the addition of an NK_1RA, such as aprepitant and fosaprepitant, to antiemetic chemotherapy regimens has improved management of acute nausea/vomiting. Currently available NK_1RAs include aprepitant, fosaprepitant, netupitant, and rolapitant. Most prophylaxis regimens with 5-HT_3 antagonists also contain dexamethasone 10-20 mg IV daily, as dexamethasone further enhances its efficacy of antiemetic control, and is now considered the standard of therapy in HEC [8,9].

In a study combining aprepitant, palonosetron, and low-dose dexamethasone prior to conditioning regimens for autologous hematopoietic stem cell transplant, none of 18 analyzed patients had emetic failure and complete control was achieved in 78 % in the acute phase, 33% in delayed, and 17% in extended phases.[10] Yet, nausea continued to occur in 78%, albeit not to a significant degree in 61%.[10] This study helped establish the triple regimen as standard of care over the prior standard of ondansetron and dexamethasone where emesis is prevented in only 4-20% of patients.[10] While demonstrating a significant improvement, CINV continues to be inadequately managed (78% with some nausea), especially in delayed-onset nausea and vomiting (77% with delayed emesis).

Inadequate nausea control contributes to the morbidity of HSCT with persistence of common side effects of conditioning regimens for bone marrow or stem cell transplant. CINV can impair nutrition, exacerbate mucositis, and overall negatively impact upon patients' quality of life and functional capacity.

2.2 Study Agents

NEPA (300 mg netupitant/0.5 mg palonosetron), commercially available as Akynzeo®[11], is an oral fixed dose combination product of netupitant, a substance P/neurokinin 1 (NK_1) receptor antagonist, and palonosetron hydrochloride, a serotonin-3 (5-hydroxytryptamine 3; 5HT_3) receptor antagonist (RA). Both netupitant and palonosetron hydrochloride are anti-nausea and antiemetic agents.

Each NEPA (Akynzeo®; 300 mg netupitant/0.5 mg palonosetron) capsule is composed of one white-caramel hard gelatin capsule which contains three tablets each containing 100 mg netupitant and one gelatin capsule containing 0.56 mg palonosetron hydrochloride (equivalent to 0.50 mg palonosetron). The inactive ingredients are microcrystalline cellulose, sucrose fatty acid esters, povidone K-30, croscarmellose sodium, purified water, silicon dioxide, sodium stearyl fumarate, magnesium stearate, mono-and di-glycerides of capryl/capric acid, glycerin, polyglyceryl oleate, butylated hydroxyanisole (BHA), gelatin, sorbitol, titanium dioxide, yellow iron oxide, and red iron oxide. It may contain traces of medium-chain triglycerides, lecithin, and denatured ethanol.

NEPA Pharmacology

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK_1) receptors, and palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors.

The receptor occupancy for the CINV dosing regimen of netupitant was measured in a human Positron Emission Tomography (PET) study. Netupitant was shown to cross the blood brain barrier with a NK_1 receptor occupancy of 92.5%, 86.5%, 85.0%, 78.0%, and 76.0% in striatum at 6, 24, 48, 72, and 96 hours, respectively, after administration of 300 mg netupitant. Co-administration of single dose netupitant 600 mg and palonosetron 1.5 mg had no significant effects on the QTc interval.

NEPA Pharmacokinetics

After single dose administration of NEPA (Akynzeo) in healthy subjects, the peak plasma concentrations for netupitant and palonosetron were reached in about 5 hours. When administered under fed condition, the systemic exposure to netupitant and palonosetron was similar to those obtained under fasting condition. In cancer patients who received a single dose of NEPA (Akynzeo®) 1 hour prior to chemotherapy (docetaxel, etoposide, or cyclophosphamide), the C_{max} and AUC of netupitant and its metabolites were similar to those in healthy subjects. The mean C_{max} and AUC of palonosetron in cancer patients were similar to those in healthy subjects. No significant changes in pharmacokinetics of netupitant and palonosetron were observed when 450 mg oral netupitant and 0.75 mg oral palonosetron were co-administered.

NEPA Elimination

Following administration of a single oral 0.75 mg dose of [^{14}C]-palonosetron to six healthy subjects, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in feces. The amount of unchanged palonosetron excreted in the urine represented approximately 40% of the administered dose. In cancer patients, t½ was 48 ± 19 hours. After a single-dose of approximately 0.75 mg intravenous

palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 mL/h/kg (mean ± SD) and renal clearance was 66.5 ± 18.2 mL/h/kg.

Netupitant inhibits CYP3A4, thus caution with co-administration of CYP3A4 inducers/inhibitors/substrates should be followed.[12] However, there was no significant interaction observed between netupitant and palonosetron, thus the primary effect of NEPA on CYP3A4 inducers/inhibitors/substrates was similar to what is seen with netupitant alone [12].

Netupitant

Netupitant is chemically described: 2-[3,5-bis(trifluoromethyl)phenyl]-N, 2 dimethyl-N-[4-(2methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl] propanamide. The empirical formula is C30H32F6N4O, with a molecular weight of 578.61. Netupitant exists as a single isomer, is white to off-white crystalline powder, and is freely soluble in toluene and acetone, soluble in isopropanol and ethanol, and very slightly soluble in water.

Netupitant Absorption

Upon oral administration of a single dose of netupitant, netupitant started to be measurable in plasma between 15 minutes and 3 hours after dosing. Plasma concentrations reached C_{max} in approximately 5 hours. There was a greater than dose-proportional increase in the systemic exposure with the dose increase from 10 mg to 300 mg and a dose-proportional increase in systemic exposure with a dose increase from 300 mg to 450 mg.

Netupitant Distribution

In cancer patients netupitant disposition was characterized by a large apparent volume of distribution (V_z/F: 1982 ± 906 L) (mean ± SD). Human plasma protein binding of netupitant is greater than 99.5% at drug concentrations ranging from 10-1300 ng/mL and protein binding of its major metabolites (M1, M2 and M3) is greater than 97% at drug concentrations ranging from 100 to 2000 ng/mL.

Netupitant Metabolism

Once absorbed, netupitant is extensively metabolized to form three major metabolites: desmethyl derivative, M1; N-oxide derivative, M2; and OH-methyl derivative, M3. Metabolism is mediated primarily by CYP3A4 and to a lesser extent by CYP2C9 and CYP2D6. Metabolites M1, M2 and M3 were shown to bind to the substance P/neurokinin 1 (NK1) receptor.

Mean C_{max} was approximately 11%, 47% and 16% of netupitant for metabolites M1, M2 and M3, respectively. Mean AUC for metabolites M1, M2 and M3 was 29%, 14% and 33% of netupitant, respectively. The median T_{max} for metabolite M2 was 5 hours and was about 17-32 hours for metabolites M1 and M3.

Palonosetron

Palonosetron hydrochloride is chemically described: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride. The empirical formula is C19H24N2O.HCl, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer, is a white to off-white crystalline powder, and is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

Palonosetron Absorption

Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97%. After single oral doses using buffered solution mean maximum palonosetron concentrations (Cmax) and area under the concentration-time curve (AUC0-∞) were dose proportional over the dose range of 3.0 to 80 µg/kg in healthy subjects.

Palonosetron Distribution

Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg. Approximately 62% of palonosetron is bound to plasma proteins.

Palonosetron Metabolism

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 RA activity of palonosetron. In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

2.3 Other Agents

Dexamethasone 12 mg 1 hour prior (+/- 30 minutes) to chemotherapy on Day 1, then 8 mg PO daily on days 2 through 6. Dexamethasone will not continue on day 7 (SCT Day 0), as our subjects will receive hydrocortisone with stem cell infusions as per our institutional standard. Additionally, with use of other NK1 antagonists during stem cell conditioning, our institutional protocols do not include dexamethasone on the day of stem cell infusion. Patients on strong CYP 3A4 inducers or inhibitors would need to have those agents replaced with clinical alternatives prior to beginning the study. Length of washout period will be 7 days. Benzodiazepines will not be allowed as hypnotics. Additional antiemetics will be allowed for rescue but not for prophylaxis.

2.4 Study and Dose Rationale

NEPA has been evaluated in other chemotherapy regimens, but has yet to be evaluated in HSCT conditioning regimens. Combined use of netupitant and palonosetron (NEPA) has been effective in managing CINV in single dose administration of both highly and moderate emetogenic chemotherapies. To determine the optimal netupitant dose for future fixed-dose administration, a phase II study randomized

694 chemotherapy naïve patients to one of 5 antiemetic groups prior to receiving highly emetogenic chemotherapy (cisplatin): one of 3 doses of netupitant (100, 200 and 300 mg) with single dose palonosetron (0.5 mg), oral palonosetron alone (0.5 mg; PALO), and standard 3-day aprepitant (APR) and ondansetron; all in combination with dexamethasone.[13] The 300 mg netupitant dose with PALO was superior to lower NEPA doses and to PALO alone. Furthermore, all three NEPA arms were well tolerated and had similar safety profiles to PALO and APR.

5-HT_3 RAs were effective at reducing acute nausea and emesis, but palonosetron has been identified as the only $5HT_3$-antagonist to reduce both acute and delayed-onset nausea and vomiting.[14] Similarly, growing data suggests delayed nausea and vomiting are due to activation of the NK_1 pathway; furthermore, the long half-life of netupitant positions it well to remain effective during delayed phase nausea and vomiting.[4] The combination of netupitant and palonosetron was shown in vitro to induce a synergistic inhibition of the Substance P response in NG108-5 cells, which express both 5-HT3 and NK1 receptors.[14] Another in vitro study showed additive NK1 receptor internalization in NG108-5 cells with combined administration of netupitant and palonosetron, potentially identifying the mechanism belying this synergistic inhibition of Substance P response.[6]

NEPA has been evaluated in its current formulation in a number of settings, including its phase II trial for dosage as noted above. NEPA has been evaluated in phase III trials for both singly dosed chemotherapy and over repeated cycles for highly and moderately emetogenic chemotherapies.[1] However, it has not yet been evaluated specifically in moderately and highly emetogenic conditioning regimens for hematopoietic stem cell transplant (HSCT).

In a randomized phase III study, NEPA had a significantly higher complete response (no emesis and no rescue medication) compared with Palonosetron (PALO) alone following a moderately emetogenic chemotherapy (anthracycline-cyclophosphamide). Complete response was seen in 76.9% of NEPA patients compared with 69.5% given palonosetron. Importantly, this study included primarily women (98.2% NEPA; 97.9% PALO).[2] This study excluded those receiving highly emetogenic chemotherapy (HEC), radiation therapy, or bone marrow or stem-cell transplant.

While previously shown to be effective in single dose chemotherapy regimens, a multinational, double-blind study randomized 413 patients to receive either a single dose of NEPA and dexamethasone or a three-day dosing of aprepitant, palonosetron and dexamethasone in multiple (at least six) cycles of both MEC and HEC[1]. Again, patients were ineligible if preparing for HSCT. NEPA showed a small but consistent improvement in complete response (from 2-7%) compared with aprepitant/palonosetron over 6 chemotherapy cycles.[1]

In high-dose, highly-emetogenic chemotherapy, palonosetron needs to be dosed more frequently than netupitant due to palonosetron's approximate 40 hour half-life, in contrast with netupitant's approximate 90 hour half-life. As Einhorn et al. showed, palonosetron along with dexamethasone is effective in alternate-

day dosing in multi-day highly emetogenic cisplatin-containing regimen (BEP), where cisplatin is given over 5 days and palonosetron is given on days 1, 3, and 5.[15] The majority of patients had no emesis, moderate-to-severe nausea, or need for rescue medications. Similarly, the present study will dose NEPA on days 1, 3 and 6. Notably, NEPA will be redosed on day 6 instead of day 5 because day 6 of the BEAM regimen includes melphalan, the drug of greatest emetogenic potential in the regimen.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Subjects must be undergoing autologous or allogeneic Hematopoietic Stem Cell Transplant (HSCT) with the BEAM conditioning regimen prior to HSCT;

2. Age ≥ 18 years. Both men and women and members of all races and ethnic groups will be included;

3. ECOG performance status ≤ 2 or Karnofsky Performance Score ≥60% (see Appendix A, Appendix A2 for Karnofsky Performance Score (KPS) conversion);

4. Able to swallow oral medications;

5. Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

1. Subjects with known hypersensitivity or other allergic reactions attributed to compounds of similar biologic composition to netupitant, palonosetron, dexamethasone, or other agents used in the study.

2. Subjects who are receiving any other investigational agents or have received another investigational drug in the last 30 days.

3. Subjects who have had emesis or required antiemetics in the 48 hours prior to starting the BEAM conditioning regimen. Patients required to take antipsychotics, appetite stimulants, or other medications with antiemetic effects will also be excluded if those medications cannot be replaced by therapeutic equivalents.

4. Female subjects who are pregnant, have a positive serum hCG, or are lactating and intend to breastfeed a child. Pregnant women are excluded from this study because hematopoietic stem cell transplant conditioning regimens including the BEAM regimen have the potential for teratogenic or abortifacient effects. NEPA itself is Pregnancy Class C. Because there is an unknown but

   potential risk for adverse events in nursing infants secondary to treatment of the mother with NEPA, breastfeeding should be discontinued if the mother is treated with NEPA. These potential risks may

also apply to other agents used in this study.

5. HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with NEPA. In addition, these subjects are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in subjects receiving combination antiretroviral therapy when indicated.

6. Subjects who have taken a neurokinin antagonist within 14 days prior to beginning the BEAM regimen.

7. Subjects who have a serum creatinine > 2 x ULN.

8. Subjects with severe renal failure or End stage renal disease (estimated GFR (glomerular filtration rate) of < 30 mL/min) as estimated by the Cockcroft-Gault formula.

   Formula (Men): GFR [mL/min] = {((140 – age[y]) x body weight [kg]) / (72 * S_{Cr} [mg/dL)}

   Formula (Women): GFR [mL/min] = 0.85 * {((140 – age[y]) x body weight [kg]) / (72 * S_{Cr} [mg/dL)}

9. Subjects with severe hepatic insufficiency (Child-Pugh Score > 9).

Measure	1 point	2 points	3 points
Total bilirubin [mg/dL]	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin [g/dL]	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation [s]	<4.0	4.0–6.0	> 6.0
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

10. Subjects who have reported drinking > 5 alcoholic drinks daily for the last year.

11. Subjects who have concurrent illness requiring systemic corticosteroid use other than the planned dexamethasone during conditioning therapy.

12. Subjects with gastrointestinal conditions that might result in malabsorption of the study drug.

13. Subjects with a history of anxiety-induced ("anticipatory") nausea and vomiting.

14. Subjects on strong CYP 3A4 inducers or inhibitors who are unable to have those agents replaced

with clinical alternatives prior to beginning the study. Length of washout period will be 7 days. Notably, in the case of allogeneic transplant recipients requiring cyclosporine or tacrolimus, no empiric dose adjustments will be required due to close level monitoring and adjustments that are standard in OHSU protocols.

15. Subjects unable to discontinue benzodiazepines as antiemetics will not be allowed. Additional antiemetics will be allowed for rescue but not for prophylaxis.

16. Subjects with personal or family history of QT prolongation, uncorrected electrolyte abnormalities, congestive heart failure, bradyarrhythmia, conduction disturbances, and those taking anti-arrhythmic medicinal products or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Relevant information will be collected as part of subject medical history.

4.0 REGISTRATION PROCEDURES

4.1 Subject Registration

Participants will be required to give written informed consent to participate in the study before any screening tests or evaluations are conducted that are not part of standard care.There is no randomization for treatment. This is a phase II trial with an intention-to-treat all patients who are enrolled in this clinical trial. Potential subjects will be seen by investigators of this study as a new patient or consult visit or as a follow-up visit.

4.2 Local Registration

Registrations from all consented subjects must be entered into the electronic Clinical Research Information System (eCRIS). This trial is registered with ClinicalTrials.gov and the Clinical Trials Reporting

Program (CRTP) of the National Cancer Institute (NCI). This study will use using an electronic data capture (EDC) system on OHSU secure servers [electronic case report form (eCRF)], and patient information will be entered into the eCRF in real time. Registration of OHSU patients will include the minimum of the following:

- A completed Eligibility Checklist signed by the investigator
- Signed copies of the most recent IRB-approved, informed consent form including HIPAA authorization.

5.0 TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered either inpatient or outpatient. Reported adverse events and potential risks associated with NEPA (netupitant/palonosetron) and dexamethasone are described in Section 7. No dose modifications for NEPA and dexamethasone are planned in this protocol. No investigational or commercial antiemetic agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy. The study regimen is described below:

NEPA 300 mg/0.5 mg PO will be administered 60 minutes (+/-30 minutes) prior to chemotherapy on Day 1, Day 3, and Day 6.

Dexamethasone 12 mg PO will be given 60 minutes (+/-30 minutes) prior to chemotherapy on Day 1 and 8 mg PO will be given on each additional day of conditioning chemotherapy (Days 2 through 6). Due to netupitant interaction with dexamethasone, see section 7.2.1, this dose is equivalent to the standard dexamethasone dose of 20 mg/day. Dexamethasone will only be given on days that chemotherapy is received.

HSCT Conditioning Regimen

BEAM HSCT chemotherapy conditioning regimen:

- Carmustine* 300 mg/m2 IV on Day 1
- Etoposide 200 mg/m2/day IV days 2 through 5
- Cytarabine 400 mg.m2/day IV on days 2 through 5
- Melphalan 140 mg/m2 IV on day 6

*In patients with BMI 30 or higher, BEAM dosing will be per standard of care and the ASBMT guidelines for obese patients. Dosing for Carmustine is based on a 40% adjusted body weight.

5.2 Distribution

A study investigator's order will be entered into BEACON and sent to the investigational drug pharmacy. The pharmacy will supply the nursing floor with unit dose capsules.

The doses are to be administered on the nursing floor by a research nurse and documented in the patient's

medical record. If the dose is unused, the medication will be returned to the investigational pharmacy.

5.3 General Concomitant Medication and Supportive Care Guidelines

- All previously ordered scheduled antiemetics will be discontinued.
- Benzodiazepines will not be allowed as hypnotics.
- Drugs interacting with NEPA are not allowed on study. Patients previously taking drugs that interact with NEPA, such as those metabolized through the cytochrome P450 system, may participate after a minimum washout period of 7 days.
- In individuals with personal or family history of long QT syndrome, anti-arrhythmic medications and or other medicinal products that lead to QT prolongation or electrolyte abnormalities will be minimized as discussed in exclusion criteria.

All patients will receive rescue antiemetics per normal procedures and number of doses of each agent will be charted on the medication administration record and tracked by type and quantity. If needed for patient comfort or safety, rescue medications may be administered on a regularly scheduled basis at the physician's discretion. The choice of rescue medications will be left to the health care provider's discretion but dose and efficacy will be tracked. The actual time of first rescue medication from the start of conditioning therapy will be noted. Because there is a potential for interaction of NEPA with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The principal investigator should be alerted if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.3 Duration of Treatment

Patients will be hospitalized per standard of care for bone marrow and peripheral stem cell transplantation. Once discharged from the hospital, patients will continue with the recommended follow-up care post transplantation in the outpatient bone marrow transplant/hematology clinic. Patients will be followed 14 days (+/- 72 hours of day 20 as in Section 5.4) after receiving their last dose of NEPA for potential adverse events. This follow up visit may occur in the clinic or in the hospital if the patient is still admitted.

5.4 Duration of Follow-up

Subjects will be monitored on study for a maximum of 20 days (11 days of initial evaluation plus end of study evaluation 14 days after receiving the final dose of NEPA). End of study corresponds with HSCT Day +13; however, for clarity all study documentation will refer to study days 1-20. End of study assessment must be performed within ±72 hours of the true day 20 (i.e. Between days 17-23). The End of

study evaluation will be completed at either the end of the study or at early termination. In the event that therapy is stopped for a life-threatening allergy, or some other unreasonable toxicity, then patients will be followed for one month from the date therapy is stopped or until the resolution of the toxicity. If the toxicity is expected to continue the patient will be followed until the stabilization of that toxicity.

5.5 Criteria for Evaluation

Nausea will be assessed daily using a self-reported QOL/nausea assessment form (CINV Questionnaire; Appendix C) beginning on admission and continuing through Study Day 10. Patients will complete a daily CINV questionnaire, noting number of episodes of emesis as well as whether they experienced nausea and to what degree (0-10). Emetic episodes will also be noted by the patient's nurse, recorded on the daily medical record, and verified for number each day with the patient. If patient reporting is discordant with nursing records and this discordance cannot be reconciled, the maximal number of episodes for a given day will be used. Either retching (visceral contraction without the expulsion of stomach contents) or emesis (visceral contraction with the expulsion of stomach contents) will be considered an emetic episode for study purposes. The actual time of first emesis from the start of conditioning therapy will be noted. The percentage of total food eaten and days of parenteral nutrition during the study period will be monitored for each patient through the patient self-reported questionnaire. Meals are ad libitum and percentage is based on each patient's desired meal. Patients will record their own number and percentage of meals eaten in the daily CINV questionnaire (Appendix C).

Definitions (assessed via daily CINV Questionnaire - Appendix C)

- ✓ No Nausea = no reported nausea and <1 on the 0-10 numerical scale.
- ✓ Mild Nausea = reported nausea and 1-3 on the 0-10 numerical scale.
- ✓ Moderate Nausea = reported nausea and 4-6 on the 0-10 numerical scale.
- ✓ Severe nausea = reported nausea and 7-10 on the 0-10 numerical scale.

Response Definitions:

- ✓ Complete Response (CR): The complete absence of emesis, mild to moderate nausea, and no rescue therapy in subjects who have received all 6 days of chemotherapy and 4 days of observation. Patients who do not complete days 1-6 will not be included in calculation of CR.
- ✓ Complete Protection (CP): CR plus no nausea
- ✓ Major Response (MR): One or two episodes of emesis on only one day with any level of nausea or no emesis with severe nausea

- ✓ Minor Response (mR): One to two episodes of emesis on > 1 day but less than 3 days with any level of nausea.
- ✓ Partial Response (PR): Emesis with 2 or fewer episodes of emesis on any one day of the conditioning regimen or fewer than 2 emetic episodes on > 3 days of the conditioning regimen.
- ✓ Treatment Failure (TF): More than 2 episodes of emesis on any one day of the conditioning regimen or 2 emetic episodes on ≥ 3 days of the conditioning regimen. Note: Emesis occurring within 2 hours of infusing DMSO containing stem cells will not be considered an antiemetic failure.

5.6 Criteria for Removal from Study

Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled. Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded in the eCRF. Should a subject or the subject's legally authorized guardian/representative decide to withdraw themselves or the subject from the study, all efforts will be made to complete and report the End of Treatment evaluations as thoroughly as possible.

A subject may be withdrawn from the study, if, in the investigator's expert medical judgment, the subject is non-compliant with the study requirements. Subjects may be withdrawn at the discretion of the Food and Drug Administration (FDA) or the investigator. A subject may also be discontinued from the study for the following reasons:

- If a patient experiences a grade 3 toxicity that is attributed to NEPA the patient will be discontinued from the study and followed until resolution of the toxicity as described in section 10.2.
- If the patient is suspicious for hepatic insufficiency as defined by having bilirubin ≥ 2.0 mg/dL a Child-Pugh Score should be calculated. If a patient develops hepatic insufficiency (Child-Pugh score > 9) then NEPA will be discontinued and they will be followed through Study Day 20 or until their score falls below 5 whichever period is longer.

5.7 Study Discontinuation

If a subject is withdrawn from the study:

- The reason(s) for withdrawal must be documented in the subject's medical record and eCRF.
- The End-of-treatment or Early Termination visit should be performed within 14 days (+/-72 hours of true day 20) of last dose.
- All subjects must be followed for safety until the time of the follow-up evaluation, until study drug related toxicities resolution , or until stabilization of the adverse event, whichever is longer.

If the sponsor investigator or regulatory authority discovers conditions during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation with

the investigators. The sponsor-investigator has the right to terminate the study at any time. Reasons for terminating the study may include the following:

- Incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Investigator(s) do not adhere to the protocol or applicable regulatory guidelines in study conduction.

6.0 DOSING DELAYS/DOSE MODIFICATIONS

NEPA dose adjustments or delays are prohibited. NEPA will be dosed under usual standard of care, including those with BMI >30 per guidance from the oncology pharmacist. NEPA does not require dose adjustment for diminished renal function. In the event of toxicity judged by the investigators to be related to the study drug, patients may be withdrawn from the study as noted in Section 5.6 and alternative antiemetics instituted for patient safety. Note that other agents which may potentially require dose adjustments due to an interaction with NEPA (see section 7.2) will be reviewed and adjusted appropriately by the oncology pharmacist.

7.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Adverse Events

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Sections 5 and 6 of the Prescribing Information for NEPA (**Appendix B**) identify known reported and theoretical potential adverse events. Occurrence of hypersensitivity reactions or serotonin syndrome as described in section 5 of the Prescribing Information would warrant expedited reporting.

7.2 DRUG INTERACTIONS

Effects of NEPA on Other Drugs

Interaction with CYP3A4 Substrates

Netupitant, a component of NEPA, is a moderate inhibitor of CYP3A4.

AKYNZEO should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. The plasma concentrations of CYP3A4 substrates can increase when co-administered with NEPA. The inhibitory effect on CYP3A4 can last for multiple days.

Dexamethasone

A two-fold increase in the systemic exposure of dexamethasone was observed 4 days after single dose of netupitant. The duration of the effect was not studied beyond 4 days. Administer a reduced dose of dexamethasone with NEPA.

Midazolam

When administered with netupitant, the systemic exposure to midazolam was significantly increased. Consider the potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) when administering these drugs with NEPA.

Interaction with chemotherapeutic agents

The systemic exposure of chemotherapy agents metabolized by CYP3A4 can increase when administered with NEPA. Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. Caution and monitoring for chemotherapeutic related adverse events are advised in patients receiving chemotherapy agents metabolized primarily by CYP3A4.

Interaction with oral contraceptives

Clinically significant effect of NEPA on the efficacy of oral contraceptives containing levonorgestrel and ethinyl estradiol is unlikely.

Effects of Other Drugs on NEPA

Netupitant, a component of NEPA, is mainly metabolized by CYP3A4.

In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron.

CYP3A4 Inducers

Avoid concomitant use of NEPA in patients who are chronically using a strong CYP3A4 inducer such as rifampin. A strong CYP3A inducer can decrease the efficacy of NEPA by substantially reducing plasma concentrations of the netupitant component.

CYP3A4 Inhibitors

Concomitant use of NEPA with a strong CYP3A4 inhibitor (e.g., ketoconazole) can significantly increase the systemic exposure to the netupitant component of NEPA. However, no dosage adjustment is necessary for single dose administration of NEPA.

Serotoninergic Drugs

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs).

7.3 Adverse Event Characteristics

CTCAE term (AE severity description and grade): The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Expectedness: Adverse Events can be 'Unexpected' or 'Expected' (see sections 5 and 6 of the current Prescribing Information attached to this document as **Appendix B** for known warnings and AEs).

Causality of the AE:

- Definite: the AE *is clearly related* to the study treatment;
- Probable: the AE is *likely related* to the study treatment;
- Possible: the AE *may be related* to the study treatment;
- Unlikely: the AE *is unlikely related* to the study treatment;
- Unrelated: the AE *is clearly NOT related* to the study treatment.

7.4 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems (UPs) and Adverse Events (AEs) will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site: http://www.ohsu.edu/xd/about/services/integrity/policies/all-irb-documents.cfm.

Unanticipated Problems and Serious Adverse Events as defined below must be reported to OHSU IRB within 5 business days after the PI learns of the event. If any of these require a change (as determined by the PI or the IRB) to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the OHSU IRB.

This study will use the Office for Human Research Protections (OHRP) definition of unanticipated problems (UPs). UPs are defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

An adverse event or suspected adverse reaction is considered "serious" if it results in any of the

following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly or birth defect.

7.5 Central Reporting of Adverse Events for Multicenter Studies

N/A

7.6 Regulatory Reporting

For this investigator-initiated study, the OHSU Principal Investigator is the study sponsor. The sponsor-investigator is required to report SAEs to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. SAEs to be reported include any unexpected (not included in

the prescribing information). SAEs occurring during clinical studies will be reported to FDA as MedWatch form (specified in the investigational new drug/biologic regulations using the FDA 3500 Voluntary Reporting form, which is available for submission online at (and also available as a pdf): http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm).
Sponsor will report to FDA any identified and validated signal originated from the study and the final study report.

7.7 Sponsor or Additional Reporting Requirements.

Sponsor (i.e. Principal Investigator) will send to Helsinn Corporate Drug Safety (**drug-safety@helsinn.com**) all the available information regarding any SAE (i.e. considered at least possibly related to NEPA), within 15 calendar days from when the Investigator first became aware of it in MedWatch format for events not considered life-threatening. Any possibly related SAE that is life-threatening or results in subject death will be reported to Helsinn within 7 calendar days, in alignment with FDA guidelines for IND Safety Reporting. Sponsor is responsible for performing signal detection as required by US regulations (Safety Assessment for IND Safety Reporting- Guidance for the Industry) and will report to Helsinn Corporate Drug Safety any signals it might identify within 3 working days from identifying them. The notification will include a report explaining which is the evidence and reason that has led sponsor to identify a signal.
Helsinn Corporate Drug Safety may ask additional information to Investigator or Sponsor regarding the received serious adverse event or safety signal to better assess it, but will not in any why try to influence Investigator's or Sponsor's causality assessment.
Sponsor will send to Helsinn the final draft of the study report and or of any publication prior to submitting it to an Authority or to a publisher.

8.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 Agent Accountability

The sponsor-investigator, or a responsible party designated by the sponsor-investigator, must maintain a careful record of the inventory and disposition of the study agent. Medication accountability for this study will be maintained by OHSU Research Pharmacy Services (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage
(See http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm).
Responsibility for drug accountability at the study site rests with the sponsor-investigator; however, the

sponsor-investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by

the study monitor and are open to inspection at any time by any applicable regulatory authorities.
The sponsor-investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study medication until the end of the study. The sponsor-investigator or designee must maintain records that document:

- Investigational product delivery to the study site
- The inventory at the site
- Use by each subject including pill/unit counts from each supply dispensed
- Return to the sponsor-investigator or designee

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study subjects. The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the subjects were provided the correct study medication specified. Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to Helsinn for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from Helsinn or Helsinn's study drug distributor.

8.2 Study Agent (Commercially available product)

Availability: NEPA (Akynzeo®) is supplied to investigators by Helsinn.
Product description: AKYNZEO® (300 mg netupitant/0.5 mg palonosetron) is an oral fixed combination product of netupitant, a substance P/neurokinin 1 (NK_1) receptor antagonist, and palonosetron hydrochloride, a serotonin-3 ($5HT_3$) receptor antagonist. Both netupitant and palonosetron hydrochloride are anti-nausea and anti-emetic agents.
Netupitant is chemically described: 2-[3,5-bis(trifluoromethyl)phenyl]-N, 2 dimethyl-N-[4-(2methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl] propanamide. The empirical formula is $C_{30}H_{32}F_6N_4O$, with a molecular weight of 578.61. Netupitant exists as a single isomer. Netupitant is white to off-white crystalline powder. It is freely soluble in toluene and acetone, soluble in isopropanol and ethanol, and very slightly soluble in water.
Palonosetron hydrochloride is chemically described: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer. Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

Each AKYNZEO® (300 mg netupitant/0.5 mg palonosetron) capsule is composed of one white-caramel hard gelatin capsule which contains three tablets each containing 100 mg netupitant and one gelatin capsule containing 0.56 mg palonosetron hydrochloride (equivalent to 0.50 mg palonosetron). The inactive ingredients are microcrystalline cellulose, sucrose fatty acid esters, povidone K-30, croscarmellose sodium, purified water, silicon dioxide, sodium stearyl fumarate, magnesium stearate, mono-and di-glycerides of capryl/capric acid, glycerin, polyglyceryl oleate, butylated hydroxyanisole (BHA), gelatin, sorbitol, titanium dioxide, yellow iron oxide, and red iron oxide. It may contain traces of medium-chain triglycerides, lecithin, and denatured ethanol.

AKYNZEO® (300 mg netupitant/0.5 mg palonosetron) capsules: hard gelatin capsules with white body and caramel cap with "HE1" printed on the body. They are supplied as follows:

- ✓ NDC # 62856-796-01: pack of one capsule in one blister
- ✓ NDC # 62856-796-04: pack of four capsules (two capsules per blister strip).

Solution preparation: Not applicable

Storage requirements: Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F).

Route of administration: Oral administration.

9.0 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

None planned

10.0 STUDY PROCEDURES AND SCHEDULE OF EVENTS

10.1 Screening/Baseline Visit

Investigator will obtain written informed consent from the patient prior to any study-driven tests or procedures. However, any tests or procedures done as part of standard care and within window per protocol may be used. All procedures must be performed prior to the first day of conditioning therapy. Screening will occur within thirty days of enrollment. This time frame is needed to facilitate pre-study screening of potential subjects, who may come from all areas of the state. Investigator will ensure that subject satisfies all inclusion and exclusion criteria prior to enrollment.

10.2 Study Treatment Visits

Each subject will be followed for a maximum of 20 days (+/-72 hours). The schedule of events in section 10.5 indicates mandatory data collected at each time point for the trial, but it is expected that additional tests/procedures or visits may occurs as standard of care, which is entirely at the discretion of the

investigator. Most subjects

will have laboratory studies and clinical evaluations outside of this schedule as part of their standard care.

10.3 End of Study/Early Termination

End of study will be at Study Day 20 (equivalent to HSCT Day +13).This assessment must be performed within ±72 hours. The End of study evaluation will be completed at either the end of study or at early termination. In the event that therapy is stopped for a life-threatening allergy, or some other unreasonable toxicity, then patients will be followed for one month or until the resolution of the toxicity. If the toxicity is expected to continue the patient will be followed until the stabilization of that toxicity.

10.4 Study Assessments and Procedures

Demographics and Medical History: Demographic data and a complete medical history will be collected during the screening periodto starting study treatment. Medical history in between visits should be documented at each study visit once study treatment has started. All transfusions including date, product transfused, number of units, and reason for transfusion should also be collected as part of the interval medical history.

Concomitant Medications: All concomitant medications and treatments must be recorded in the electronic case report form (eCRF). Any prior medication received up to 15 days prior to the Baseline visit will be recorded in the eCRF. Concomitant treatments that are required to manage a subject's medical condition during the study will also be recorded in the eCRF. Prior and/ or ongoing medications will be reviewed during screening to determine subject eligibility. The medication record will be maintained following enrollment including any changes to the dose or regimen. Prior and concomitant medication including any prescription, over the counter or natural/herbal/multivitamin preparations taken will be recorded.

Physical Exam: Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant or advanced Registered Nurse Practitioner as local law permits. The physical exam at baseline should be performed per institutional standards and standard care physical exams done prior to patient consent may be used. All other physical exams will include an evaluation of any AEs or any previously reported symptoms or prior physical examination findings.

Performance Status: ECOG or Karnofsky Performance Score will be determined and performed at screening as indicated in the schedule of events in section 10.5. Refer to Appendix A for ECOG scale and Karnofsky Performance Score conversion.

Weight: Must be collected prior to treatment with NEPA and as indicated in section 10.5 Schedule of events

Vital Signs: Resting vital sign measurements must be performed ±24 hours of target days noted in the schedule of events. Vital sign measurements must include: blood pressure, pulse, respiration rate and temperature.

Complete Blood Count: Local hematology will be collected per institutional standards and must include

at minimum a white cell count, differential, hemoglobin, hematocrit, and platelet count. Note: it is allowable to use labs from prior day for care of these patients, as daily labs are often performed immediately prior to midnight.

Chemistry: Local chemistry will be collected per institutional standards and must include at minimum the following: sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, glucose, calcium, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, albumin, total bilirubin. Note: it is allowable to use labs from prior day for care of these patients, s daily labs are often performed immediately prior to midnight.

Pregnancy Test: A urine pregnancy test is required for all female subjects during screening for women of childbearing potential. If the urine pregnancy test is positive, serum pregnancy tests must be performed per institutional standards.

Adverse Event assessments: Toxicities and adverse experiences will be assessed at each visit using the NCI Common Toxicity Criteria for Adverse Events 4.03 (CTCAE). Adverse event collection will begin when subject takes their first dose of study drug and continues until the subject completes the End of Study visit or until one month following toxicity on trial, whichever comes later (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All AEs at CTCAE grade 3 or 4 and All AEs related to gastrointestinal symptoms of any CTCAE grade for AEs should be recorded in the eCRF.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental 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.

Adverse events are collected and summarized after the completion of each patient's study period. As noted previously, SAEs are assessed immediately and reported within 24 hours. Non-SAE adverse events will be closely evaluated after the initial 13 patients, and the results will be included in the determination of study continuation. If not previously reported product-related, treatment-emergent, adverse events are prominent in this patient group, the clinical trial medical personnel (MDs) will determine if they are sufficient to require study cessation in the event that study efficacy end points are being met, which would otherwise allow study progression to the full patient complement. If such events are present and the decision is made

to proceed, additional information will be provided to the CRRC and IRB for their examination and review.

CINV Questionnaire: Nausea will be assessed daily using the patient self-reported CINV Questionnaire; Appendix C) beginning on Day 1 and continuing through Day 11 (HSCT Day

+4).

10.5 Schedule of Events

Visit	Screening	1	2	3	4	5	6	7	8	9	10	11	End of Study/ Early Term
Day	**-30**	**1**	**2**	**3**	**4**	**5**	**6**	**7 HSCT**	**8**	**9**	**10**	**11**	**20**
Countdown to HSCT		**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0 HSCT**	**+1**	**+2**	**+3**	**+4**	**+13**
Informed consent	X												
Demographics	X												
Medical history	X												
Concurrent meds	X		X----------					--X				X	
Physical exam	X												X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X												
Performance status	X												
CBC	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
NEPA (Study Agent) Administration[1]		X		X			X						
Dexamethasone Administration[2]		X	X	X	X	X	X						
HSCT Conditioning[3]		X	X	X	X	X	X						
Carmustine		X											
Etoposide			X	X	X	X							
Cytarabine			X	X	X	X							
Melphalan							X						
Adverse event evaluation			X----------										----------X
CINV Questionnaire	X[4]	X[4]	X----------								X	X	
β-hCG (female pts only)	X												

[1] 300mg/0.5mg
[2] 12mg on Day -6, 8mg on Days -5, -4, -3, -2, and -1
[3] *HSCT Conditioning: Carmustine (*300mg/m^2*), Etoposide (200 mg/m^2), Cytarabine (400 mg/m^2), Melphalan (140 mg/m^2)*
[4] *The baseline CINV Questionnaire can be administered at either Screening or Visit 1*

11.0 MEASUREMENT OF EFFECT

Nausea will be assessed daily using the patient self-reported CINV Questionnaire (Appendix C) beginning on admission and continuing through Study Day 11. Emetic episodes will be noted by the patient's nurse and recorded on the daily medical record. They will be verified for number each designated visit day with the patient. Either retching (visceral contraction without the expulsion of stomach contents) or emesis (visceral contraction with the expulsion of stomach contents) will be considered an emetic episode for study purposes. The actual time of first emesis from the start of conditioning therapy will be noted.

The percentage of each meal eaten and days of parenteral nutrition during the study period will be monitored for each patient. Meals are ad libitum and percentage is based on each patient's desired meal. Patients will record their own number and percentage of meals eaten in the CINV Questionnaire (Appendix C).

11.1 Definitions (assessed via a daily CINV Questionnaire)

11.1.1 No Nausea = no nausea and < 1 on the 0-10 numerical scale.

11.1.2 Mild Nausea = reported nausea and 1-3 on the 0-10 numerical scale.

11.1.3 Moderate Nausea = reported nausea and 4-6 on the 0-10 numerical scale.

11.1.4 Severe nausea = reported nausea and 7-10 on the 0-10 numerical scale.

11.2 Response Definitions:

11.2.1 Complete Response (CR): The complete absence of emesis, mild to moderate nausea, and no rescue therapy in subjects who have received all 6 days of chemotherapy and 4 days of observation. Patients who do not complete days 1-6 will not be included in calculation of CR. Any use of rescue medications in any subject without emesis and minor to moderate nausea will reclassify the patient from CR to MR.

11.2.2 Complete Protection (CP): CR plus no nausea

11.2.3 Major Response (MR): One or two episodes of emesis on only one day with any level of nausea or no emesis with severe nausea

11.2.4 Minor Response (mR): One to two episodes of emesis on > 1 day but less than 3 days with any level of nausea.

11.2.5 Partial Response (PR): Emesis with 2 or fewer episodes of emesis on any one day of the conditioning regimen or fewer than 2 emetic episodes on > 3 days of the conditioning regimen.

11.2.6 Treatment Failure (TF): More than 2 episodes of emesis on any one day of the conditioning

regimen or 2 emetic episodes on ≥ 3 days of the conditioning regimen. Note: Emesis occurring within 2 hours of infusing DMSO containing stem cells will not be considered an antiemetic failure.

12.0 DATA REPORTING/REGULATORY REQUIREMENTS

12.1 Data Collection and Storage

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system stored and maintained on OHSU secure servers, which facilitates information being stored in a unified format and location. To further preserve confidentiality, PHI in the EDC system will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Quality assurance will be conducted as outlined in section 12.8 under data safety and monitoring.

12.2 Privacy, Confidentiality, and Data Security (required)

Original data collection sheets will be maintained as noted above. Only research staff will have access to the patient database for data entry and subsequent data analysis. All computers have locking workstations including the most recent versions of the PGP desktop which prevents access by unauthorized staff. No data will be saved to a flash drive. All data will be de-identified once data collection is complete and no identifiable patient information will be used for subsequent publications or presentations

12.3 Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute (CI) Clinical Research Review Committee (CRRC) and the appropriate Institutional Review Board (IRB) prior to any subject being consented on this study.

12.4 Informed Consent

Written informed consent will be obtained from all subjects or the legally authorized representative of the subject participating in this trial, as stated in the Informed Consent section of the Case of Federal Regulations, Title 21, Part 50. If a subject's signature cannot be obtained, and for all subjects under the age of 18, the investigator must ensure that the informed consent is signed by the subject's legally authorized representative. If a patient is not primary English-speaking, a translator and witness will be present and the subject may sign OHSU's respective primary language consent short form after the full consent has been translated.

A documented telephone consent may be obtained in cases where a subject may be unavailable for onsite consent due to subject resources or distance from site and where primary investigator considers telephone consent appropriate. Subject will undergo identity verification by full name and date of birth and confirmation they will need to sign consent form at their next site visit. Patient will not undergo any study-driven labs or procedures outside standard of care prior to signing physical consent form.

For both onsite and telephone initial consent, the consent process will be documented. At the time of onsite consent, subject will receive a copy of their signed consent form, a copy of the signed consent will be maintained in the subject's medical record, and the original signed consent form will be maintained in the subject study binder.

12.5 Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the subject. In that event, the investigator

must notify the CRRC and IRB in writing within 10 working days after the implementation. Investigators holding the IND must notify FDA of substantive changes to the protocol.

12.6 Maintenance of Records

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to OHSU Knight Cancer Institute Clinical Trials Office. Records must be maintained according to sponsor or FDA requirements.

12.7 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.8 OHSU Knight Cancer Institute Data and Safety Monitoring Plan

In addition to complete study and pharmacy files, complete records must be maintained on each subject treated on this protocol. OHSU Knight Cancer Institute, through the auditing function of the Knight Clinical Trials Office, is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies and in accordance with the Data and Safety Monitoring Plan policies and procedures here.

Locally initiated studies will be audited by OHSU Knight CI Auditor. Newly approved studies may be audited any time after enrollment has been initiated. Each OHSU Knight approved treatment protocol will be audited on an annual basis in accordance with the Knight Data and Safety Monitoring Plan.

12.9 Inclusion of Women, Minorities and Children

12.9.1 Inclusion of Women and Minorities

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied.

The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon

Table 1: Population Demographics - Oregon (%)

Ethnic Category	**Sex/Gender**		
	Females	Males	Total
Hispanic or Latino			11.7
Not Hispanic or Latino			88.3
Ethnic Category: Total of all subjects*			100*
Racial Category			
American Indian or Alaskan Native			1.4
Asian			3.7
Black or African American			1.8
Native Hawaiian or other Pacific Islander			0.3
White			83.6
More than one race			3.8

Unknown/Other			5.3
Racial Category: Total of all subjects*			100*
TOTALS	50.4	49.6	100*

Source: Adapted from U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding

Table 2: Projected Accrual for the Present Study

Ethnic Category	**Sex/Gender**			
	Females	Males	Unknown	Total
Hispanic or Latino	2-3	2-3		5
Not Hispanic or Latino	19	19		38
Unknown	0-1	0-1		
Ethnic Category: Total of all subjects*	21-22	21-22		43*
Racial Category				
American Indian or Alaskan Native	0-1	0-1		0-1
Asian	0-1	0-1		1-2
Black or African American	0-1	0-1		0-1
Native Hawaiian or other Pacific Islander	0-1	0-1		0-1
White	18	18		36
More than one race	0-1	0-1		1-2
Unknown	0-1	0-1		1-2
Racial Category: Total of all subjects*	18-24	18-24		43*

Source: Adapted from U.S. Census Bureau, 2010 *Totals may not equal 43 due to rounding

12.9.2 Inclusion of Children

In accordance with NIH guidelines on the inclusion of children as participants in research involving human subjects, children under the age of 18 years must be included in all human subjects' research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them. Therefore, proposals for research involving human subjects must include a description of plans for the inclusion of children.

This protocol does not include children for the following reason: 1. The number of children with this type of cancer is limited. 2. Additionally, no dosing or adverse event data are currently available on the use of this study agent in this way in subjects <18 years of age, therefore, children are excluded from this study but will be eligible for future pediatric trials with this study agent.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a Phase II clinical trial designed according to Simon's two-stage optimum design. The initial stage will enroll 13 subjects. If 3 or fewer subjects obtain a complete response

(defined as no emesis or rescue therapy during 0-264 hours), the trial will be stopped due to futility. If 4 or more subjects show a complete response, an additional 30 patients will be enrolled for a total planned enrollment of 43 subjects. This design has 80% power and one-sided 5% significance level to detect a complete response rate of 20% (historical rate) vs. 40% (desired rate).

13.2 Primary and Secondary Endpoints

A primary endpoint is Complete Response (CR) defined as no emesis and no rescue therapy for hours 0-264, 6 days of chemotherapy and 5 days post chemotherapy.

A secondary endpoint is CR for hours 0-144 (Acute phase), CR for hours 145-264 (delayed phase), and Complete Protection (CP) rate defined as CR plus no nausea for hours 0-144, 145-264, and the whole period.

13.3 Analysis Populations

An intent to treat (IIT) analysis set consists of all patients consented and enrolled regardless of the receipt of the study drug or completion of CINV assessments. The IIT analysis set is used to report the trial accrual. A safety analysis set consists of IIT patients who receive at least one dose of the study drug. The safety analysis set is used for safety evaluation. An efficacy analysis set consists of any patient who completes 4 or more days of this trial (i.e., receives 2 doses of NEPA), and the efficacy analysis set is used for the assessment of efficacy.

13.4 Statistical Analysis Plan

13.4.1 Analysis of Primary Endpoint

We will provide an estimate of CR and 95% confidence interval. Where appropriate, data visualization techniques will be used to graphically present the CR and CP rates over time.

13.4.2 Analysis of Secondary Endpoints

The proportion of patients with CR and CP for each time period will be provided along with 95% confidence interval. As exploratory analyses, the number of emetic episodes and rescue agents taken per patient for 264 hours from start of therapy and as well as the number occurring in 0-24 hours and 0-144 hours (acute phase) vs. those which occur between 145-264 hours (delayed phase) from chemotherapy administration will be reported descriptively. Mean levels of nausea per day and median time to worse level of nausea via the CINV Questionnaire will be computed and reported descriptively. Time to first emesis and time to first rescue will be depicted via Kaplan-Meier curves showing the percentage of patients who had no emesis or rescue medication use for the acute and delayed time periods. Ability to take in oral nutrition and fluids and changes over the 5 day period will be calculated via reports from the CINV Questionnaire and reported descriptively.

13.4.3 Interim Analyses and Stopping Rules

The trial will enroll 13 patients in Stage I. If the number of patients with CR is 3 or fewer, the trial will be closed due to futility (i.e., CR rate is unlikely to be 40%, the desired CR

rate). Otherwise, the trial will continue until a total of 43 patients are enrolled. NEPA is considered promising and worth further investigation if there are 13 or more CRs among 43 patients (i.e., CR rate significantly better than the standard of care).

Safety and tolerability will be assessed via review of adverse events (AEs), vital signs, and laboratory values. Incidence of Grade 3 or higher NEPA related toxicity will be estimated along with 95% confidence interval for each major organ system defined in NCI CTCAE v4.03.

13.5 Sample Size and Power

The complete planned study set is of 43 total patients. As above, 13 initial patients in Stage I will identify utility vs futility of this study, with a plan to proceed to the full 43 patient population (additional 30 subjects) if CR is 4 or more in Stage I. With a historical CR rate of 20% with standard of care compared with the desired NEPA response rate of 40% with 5% significance level and 80% power, 43 total subjects would adequately power this study.

13.6 Randomization Method

N/A; non-randomized

13.7 Handling of Missing Data

If a patient is unavailable for prompt evaluation we would accept an evaluation within a 24 hour period due to medical necessity or patient inability to complete the CINV Questionnaire form. Days missed will be reported and evaluated separately at the end of the study. If a patient is unable to complete the form due to illness, we will attempt to support form completion with minimal assistance from study personnel or caregivers (e.g. verbal instructions to circle their selection). For any patient who is unable to complete the CINV Questionnaire on the first 6 days of chemotherapy, those patients will be censored and replaced with another study subject for complete enrollment, as those days are considered vital for efficacy assessment. For patients who are unable to complete the form on days 7-10, study results will be noted separately in the final manuscript but will not be censored from the trial. Patients who complete 7 but fewer than 10 days of the CINV Questionnaire for any reason will be assessed in a secondary analysis. However if these occur in stage I the PI will assess the reason for non-completion and determine whether they are considered non-responders (e.g. too nauseated to fill out the form) vs. unable to complete the form for medical, scheduling, or other reasons outside of study controls. The latter patients would be replaced to support the stage I analysis, as it is crucial to ongoing study procedures but would not be replaced in stage II.

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APPENDIX A

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	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
Normal activity with effort	80	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
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Severly disabled. Hospitalisation indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalisation necessary. Active supportive	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
treatment necessary			
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Dead	0	5	Dead

As published in Am. J Clin. Oncol.:

Oken MM, Creech RH, Tormey DC et. al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix B: NEPA Prescribing Information
https://www.akynzeo.com/media/Prescribing_Information.pdf

APPENDIX C: CINV Questionnaire

CINV Questionnaire

Study ID: _____ **Date:** ____/_____/_____	**VISIT**			
	☐Screening/V 1	☐V2 (-5)	☐V3 (-4)	☐V4 (-3)
	☐V5 (-2)	☐V6 (-1)	☐V7 (HSCT)	☐V8 (+1)
	☐V9 (+2)	☐V10 (+3)	☐V11 (+4)	

Please answer all of the questions. There are no right or wrong answers. We will ask you to complete this form every day for the first 10 days of treatment.

The following terms are used in the questionnaire:

Vomiting: the bringing up of stomach contents

Nausea: the feeling that you might vomit

1. **How much difficulty did you have falling asleep last?**
   Please **circle** the number that best answers the question.

   0 1 2 3 4 5 6 7 8 9 10

   0 = no difficulty *10 = didn't fall asleep*

Please **write** the number that you circled _____

2. **How many meals do you eat on a typical day?** _____

3. **In the past 24 hours, how many meals did you eat?** _____

4. **Of the meals you ate, what percent of the total food did you eat?**
   Please circle the number that best answers the question.

   0 10 20 30 40 50 60 70 80 90 100

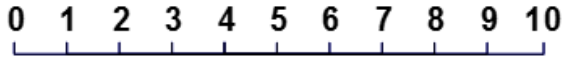
   0 = none *100 = all of my food*

   Please **write** the number that you circled. _____

5. **If you vomited in the past 24 hours, how many times did it happen?** _____

6. **In the past 24 hours, did you have any nausea?** ☐ Yes ☐ No

7. If you had any nausea, how much nausea did you have in the last 24 hours?
Please circle the number that best answers the question.



_____

0 = none *10 = as much as possible*

Please **write** the number that you circled. _____

APPENDIX D: Eligibility & Registration Checklists

Knight Cancer Institute
at Oregon Health & Science University

SUBJECT REGISTRATION & ELIGIBILITY
STUDY ID: 16288
PI: JOSEPH BUBALO

ELIGIBILITY CHECKLIST #1

SUBJECT INFORMATION	
Subject #:	Initials:

INCLUSION CRITERIA				
Each subject must meet all of the following inclusion criteria to be enrolled:				
#	**CRITERIA**	**YES**	**NO**	**COMMENTS/VALUES**
1	*Subject is undergoing autologous or allogeneic Hematopoietic Cell Transplant (HSCT) with the BEAM conditioning regimen prior to HSCT*			
2	*Age ≥ 18 years*			
3	*ECOG performance status ≤2 or Karnofsky Performance Score >60%*			
4	*Able to swallow oral medications*			
5	*Ability to understand and the willingness to sign a written informed consent document*			

Preparer's Signature: Date:

Knight Cancer Institute
at Oregon Health & Science University

SUBJECT REGISTRATION & ELIGIBILITY
STUDY ID: 16288
PI: JOSEPH BUBALO

SUBJECT INFORMATION

Subject #:	Initials:

EXCLUSION CRITERIA				
Each subject must not meet any of the following exclusion criteria:				
#	**CRITERIA**	**YES**	**NO**	**COMMENTS/VALUES**
1	*Subject has known hypersensitivity or other allergic reactions attributed to compounds of similar biologic composition to netupitant, palonosetron, dexamethasone, or other agents used in the study*			
2	*Subject is receiving any other investigational agents or has received another investigational drug in the last 30 days*			
4	*Female who is pregnant, has a positive serum hCG, or is lactating and intends to breastfeed a child. Pregnant women are excluded from this study.*			☐ N/A – Male
5	*HIV-positive on combination antiretroviral therapy*			
7	*Subject has a serum creatinine > 2 x ULN*			
8	*Subject has severe renal failure or end stage renal disease (estimated GFR of <30 mL/min using the Cockcroft-Gault formula)*			
9	*Subject has severe hepatic insufficiency (Child Pugh score > 9)*			
10	*Subject has been drinking > 5 alcoholic drinks daily for the last year*			
11	*Subject has concurrent illness requiring systemic corticosteroid use other than the planned dexamethasone during conditioning therapy*			
12	*Subject has gastrointestinal condition which might result in malabsorption of the study drug*			
13	*Subject has a history of anxiety-induced ("anticipatory") nausea and vomiting*			
15	*Subjects unable to discontinue benzodiazepines as antiemetics will not be allowed. Additional antiemetics will be allowed for rescue but not for prophylaxis.*			

16	*Subject has a personal or family history of QT prolongation, uncorrected electrolyte abnormalities, congestive heart failure, bradyarrhythmia, conduction disturbances or is taking anti-arrhythmic medicinal products or other medicinal products that lead to QT prolongation or electrolyte abnormalities.*			

(Source documentation must accompany Eligibility checklist, completed Registration and Demographics forms in order to confirm eligibility)

Date Consent Signed	
Subject Meets Eligibility Inclusion/Exclusion	☐ Yes ☐ No

Eligibility Determination

Date Screening/Baseline Assessment Collection: _____/_____/_____

	Done	**Not Done**	**Comments** • *Comment if "not done" selected* • *Enter date if different from Screening/Baseline*
Medical History	☐	☐	
Concomitant Medications	☐	☐	
Physical Exam	☐	☐	
ECOG or Karnosky Performance Score	☐	☐	
Weight	☐	☐	
Vital Signs	☐	☐	
Pregnancy Test	☐	☐	
Complete Blood Count (CBC)	☐	☐	
Chemistry Panel (CMP)	☐	☐	

Preparer's Signature:	Date:

Date of Birth	___	Age at time of study entry	_____
Sex		☐ Female ☐ Male	
Race (Check One)		☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Caucasian or White ☐ More than one race ☐ Native Hawaiian or Other Pacific Islander ☐ Other Specify_____	
Ethnicity		☐ Hispanic or Latino ☐ Non-Hispanic	

Subject entered into OHSU Clinical Research Information System?	☐ Yes ☐ No

INVESTIGATOR NAME	
INVESTIGATOR SIGNATURE	
DATE	

Preparer's Signature:	Date:

ELIGIBILITY SUMMARY #1
☐ **ELIGIBLE** ☐ **INELIGIBLE**; subject is a screen fail ☐ **INELIGIBLE**; waiver granted. Criteria and rationale: _____ _____ _____ _____

SPONSOR-INVESTIGATOR NAME	**Joseph Bubalo**
SPONSOR-INVESTIGATOR SIGNATURE	
DATE	

Preparer's Signature:	Date:

ELIGIBILITY CHECKLIST #2

SUBJECT INFORMATION	
Subject #:	Initials:

EXCLUSION CRITERIA				
Each subject must not meet any of the following exclusion criteria:				
#	CRITERIA	YES	NO	COMMENTS/VALUES
3	*Subject has had emesis or required anti-emetics in the 48 hours prior to starting the BEAM conditioning regimen. Also, patient required to take antipsychotics, appetite stimulants, or other medications with anti-emetic effects will be excluded if those medications cannot be replaced by therapeutic equivalents*			
6	*Subject has taken a neurokinin antagonist within 14 days prior to beginning BEAM regimen*			
14	*Subject is on strong CYP3A4 inducers or inhibitors and is unable to have those agents replaced with clinical alternatives prior to the beginning of the study. Length of washout period will be 7 days. In the case of allogeneic transplant recipients requiring cyclosporine or tacrolimus, no empiric dose adjustments will be required due to close level monitoring and adjustments, which are standard OHSU protocols.*			

Preparer's Signature:	Date:

INVESTIGATOR NAME	
INVESTIGATOR SIGNATURE	
DATE	

ELIGIBILITY SUMMARY #2
☐ **ELIGIBLE** ☐ **INELIGIBLE**; subject is a screen fail ☐ **INELIGIBLE**; waiver granted. Criteria and rationale:_____ _____ _____ _____

SPONSOR-INVESTIGATOR NAME	**Joseph Bubalo**
SPONSOR-INVESTIGATOR SIGNATURE	
DATE	

Preparer's Signature:	Date: