Fixed-Dose Netupitant and Palonosetron for Chronic Nausea and Vomiting in Cancer Patients

Principal Investigator: Dr. David Hui
Co-Principal Investigator: Dr. Eduardo Bruera
Collaborators: Dr. Sriram Yennu, Dr. Shalini Dalal, Sapna Amin, PharmD, Dr. Colleen Gallagher, Dr. Ahmed Kaseb, Dr. Michael Overman, Dr. Milind Javle, Dr. Kanwal P. Raghav
Biostatistics Collaborators: Diane Liu, Minjeong Park

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A. Study Objectives

Primary objective:

To estimate the efficacy (i.e. change in nausea numeric rating scale [NRS] from baseline between day 5-15) of fixed dose netupitant and palonosetron (NEPA) for chronic nausea in cancer patients.

Secondary objective:

1. To assess the secondary outcomes (e.g. proportion of patients who achieved their personalized nausea goal, antiemetic use, nausea episodes duration/frequency) for NEPA vs. placebo.
2. To assess the adverse effects associated with NEPA and placebo.

B. Background

B.1. Significance of Chronic Nausea in Cancer Patients. Nausea is defined as "an unpleasant sensory and emotional experience, which may be described in terms of a sick feeling with or without a sense of impending vomiting/retching - often associated with a perception of epigastric or upper abdominal unpleasantness or awareness".[1] Chronic nausea is defined as nausea of 1 month or greater.[2,3] In one systematic review of 39 studies consisting of 24263 patients with incurable cancer, nausea occurred in 31% (95% confidence interval [CI] 27-35%) of patients, and vomiting in 20% (95% CI 17-22%).[4] In another systematic review of far advanced cancer patients, the prevalence of nausea was estimated to be 6-68%.[5] Rhondali et al. reported that among 444 cancer patients seen at the supportive care clinic at MD Anderson Cancer Center, 112 patients had moderate/severe chronic nausea of >=4/10 in intensity.[6] 68/112 (61%) patients had a response (defined as 30% improvement from baseline) to the multimodal therapies offered by the palliative care team (e.g. metoclopramide, ondansetron, other anti-emetics, constipation management, counseling) at the followup visit 2 weeks later.

Nausea is a highly distressing symptom among cancer patients. Acutely, nausea is often accompanied by physiologic changes driven by the autonomic nervous system, such as tachycardia/bradycardia, hypersecretion of the upper gastrointestinal tract, and relaxation of the gastric fundus/cardia, diaphoresis, and skin pallor.[7] Chronically, nausea is often associated with vomiting, anorexia, cachexia, early satiety, compromising oral intake and quality of life.

Patients undergoing cancer treatments are particularly likely to experience nausea and vomiting.[8] Chemotherapy-induced nausea and vomiting (CINV), radiation-induced nausea and vomiting, and post-operative nausea and vomiting are well characterized syndromes.[9,10] Outside of the cancer treatment setting, some patients may experience chronic nausea related to early satiety, constipation, bowel obstruction, and other medications such as opioids.[11]

B.2. Pathophysiology of nausea and vomiting. Much of our understanding of the pathophysiology of nausea and vomiting is based on animal studies conducted within the framework of chemotherapy-induced nausea and vomiting (CINV).[12] Nausea and vomiting is mediated by both peripheral and central stimuli. Peripherally, disturbance in

the gastrointestinal tract results in the release of a variety of mediators by enteroendocrine cells located in the gastrointestinal mucosa, such as 5-hydroxytryptamine (5-HT), substance P, and cholecystokinin. These mediators then bind to 5-hydroxytryptamine3 (5-HT3), neurokinin-1, and cholecystokinin-1 receptors at the terminal ends of the vagal afferents that terminate in the nucleus tractus solitaries in the dorsal brain stem, which subsequently activates the central pattern generator in the medulla. Centrally, chemotherapeutic agents, opioids and or humoral stimuli may bind to receptors in the chemoreceptor trigger zone in area postrema located at the fourth ventricle, directly activating the emetic reflex. Inputs from the limbic system (amygdala), vestibular system, cerebellum, glossopharyngeal nerve, and higher cortical centres also contribute to modulate the nausea sensation and vomiting response centrally.

B.3. The Current Management of Chronic Nausea. A systematic review highlighted the paucity of robust studies to inform the management of nausea and/or vomiting unrelated to chemotherapy or radiation. Among the 93 studies on this topic, 14 were RCTs. Table 1 includes the key randomized trials on chronic nausea to date. Metoclopramide had modest evidence based on randomized controlled trials and prospective cohort studies. There were also some evidence to support the use of octreotide, dexamethasone and hyoscine butylbromide for nausea related to bowel obstruction. The authors concluded that "there are discrepancies between antiemetic studies and published antiemetic guidelines, which are largely based on expert opinion. Antiemetic recommendations have moderate to weak evidence at best. Prospective randomized trials of single antiemetics are needed to properly establish evidence-based guidelines."[13]

Table 1. Randomized Controlled Trials on Antiemetics for Chronic Nausea and Vomiting

Study	Patients	Design	Interventions	Outcome
Bruera et al. Cancer 1994 [22]	N=34 Advanced cancer Nausea >1month	DB-RCT crossover	Metoclopramide CR 40 mg q12h vs. metoclopramide IR 20 mg q6h x3d then crossover	Nausea VAS on day 3:15 vs. 8 P=0.047
Bruera et al. JPSM 2000 [2]	N=26 Advanced cancer Nausea >1month	DB-RCT crossover	Metoclopramide CR 40 mg q12h vs. placebo x4d then crossover	Nausea VAS on day 4:17 vs. 12
Bruera et al. JPSM 2004 [23]	N=51 Nausea >2w despite 48h of metoclopramide	DB-RCT	Metoclopramide 60 mg daily + either dexamethasone 20 mg daily or placebo x7d	Nausea NRS on day 3: 4.5 vs. 2.9 (P=0.16), day 8: 5.9 vs. 5.9 (P=0.85)
Corli et al JPSM 1995 [24]	N=30 Advanced cancer	DB-RCT, crossover	Levosulpride 75mg daily vs. metoclopramide 30 mg daily x7d	Hours with nausea 1.8 vs. 2.01, nausea **VAS** 0.75 vs. 1.42, (P=0.0004)
Hardy et al. SCC 2002 [25]	N=92 Opioid induced nausea	DB-RCT	Ondansetron 24 mg daily, metoclopramide 10 mg TID vs. placebo x1d	Complete control of nausea: 17%, 36%, 23% (P=NS) Early termination
Brown et al. AJHPC 1992 [26]	N=6 Hospice	OL-RCT	Acupressure wrist band, placebo wrist band, no wrist band	Not effective
Mystakidou et al. Oncologist 1997 [27]	N=120 Far advanced cancer despite metoclopramide	OL-RCT	Metoclopramide + dexamethasone, Metoclopramide + tropisetron, vs.	Total control of nausea d15: 18%, 74%, 87% Total control of vomiting 24%, 84%, 92%

			Metoclopramide + dexamethasone + tropisetron x15d	
Mystakidou et al. Cancer 1998 [28]	N=280 Far advanced cancer not bowel obstruction	OL-RCT	MET + DEX, TRO, MET + TRO, MET + DEX + TRO, DEX + CHL, TRO + CHL, DEX + TRO + CHL x15d MET 10mg QID DEX 2 mg daily TRO 5 mg OD CHL 25 mg BID	Total control of nausea d15: 18%, 66%, 74%, 87%, 18%, 74%, 85% Total control of vomiting d15: 24%, 79%, 84%, 92%, 33%, 85%, 93%

B.4. Novel Agents for Chronic Nausea

Palonosetron is a selective 5-HT3 receptor antagonist, and exerts its effect by blocking serotonin both centrally (i.e. chemoreceptor trigger zone) and peripherally (vagal nerve terminals in the periphery).[14] It also inhibits the cross-talk between the 5-HT3 and NK1 receptors. It had an elimination half-life of 48 +/- 19 hours, and T_{max} of approximately 5 hours. It is available commercially, and can be given either intravenously or orally (oral dosage form not current available in the US).

Multiple randomized controlled trials have demonstrated its efficacy in the prevention of CINV related to both moderately[15,16] and highly emetogenic regimens.[17,18] A recent meta-analyses showed statistically significant differences in favor of palonosetron compared with first-generation 5-HT3 receptor antagonists in the prevention of acute CINV, delayed CINV, and overall phase of CINV.[19]

Netupitant is a selective substance P/neurokinin (NK-1) receptor antagonist. The NK-1 receptors are located in the area postrema, the central pattern generator for vomiting and/or afferent relay station, and nucleus tractus solitarius. These areas play important roles in emesis via NK-1 receptors.[14] The absorption of netupitant is 15 minutes to 3 hours, half-life is 80 +/- 29 hours, and T_{max} is approximately 5 hours.[20,21] Currently, netupitant (parenteral and oral) is not available commercially as a stand-alone product.

Akynzeo (NEPA) is marketed as an oral fixed-dose combination of netupitant 300 mg and palonosetron 0.5 mg. Hesketh et al. conducted a double-blind randomized controlled trial in 694 patients undergoing cisplatin-based chemotherapy to examine NEPA at 3 different doses (100, 200 and 300 mg) versus palonosetron alone; an aprepitant/ondansetron group was also included in this study as an exploratory arm. The overall complete response rate (i.e. no emesis and no rescue medication 0-120 h) was 87.4%, 87.6%, 89.6%, 76.5% and 86.6%, respectively ($P<0.05$).[29] In a second study, Aapro et al. conducted a randomized controlled trial involving 1455 patients on moderately emetogenic chemotherapy. NEPA was found to be superior to palonosetron alone in achieving complete response (76.9% vs. 69.5%; $P=0.001$) in the delayed phase.[30] Gralla et al. conducted another double-blind randomized controlled safety study involving 413 patients on highly or moderately emetogenic chemotherapy..[31] The most common adverse effects of NEPA included headache, fatigue, weakness, constipation and dyspepsia.

Based on the above-mentioned studies, a recent American Society of Clinical Oncology guideline update recommended NEPA and dexamethasone as one of the options for prophylaxis of CINV among patients undergoing highly emetogenic chemotherapy regimens. Furthermore, palonosetron in combination with a corticosteroid is the preferred regimen for patients on moderately emetogenic chemotherapy.[32] Of note, neither palonosetron nor NEPA have been examined in the chronic nausea and vomiting setting.

Summary of NEPA Efficacy in Clinical Trials:
In the United States, NEPA is approved for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy (HEC). Various Phase 2 and Phase 3 studies conducted by Helsinn in patients with chemotherapy-induced nausea and vomiting have demonstrated that treatment with NEPA provides the following benefits:

- Shown to prevent of HEC-induced nausea and vomiting
- Increased response rate to the fixed dose combination in the prevention of CINV
- Akynzeo given 1 hour prior to chemotherapy is safe, well-tolerated, and efficacious as an antiemetic in the prevention of CINV

C. Pharmaceutical Information
IND Agent: NEPA (300mg Netupitant/0.5mg Palonosetron) Capsule (Refer to Investigator's Brochure for further information)

Chemical Name: 2-[3,5-Bis(trifluoromethyl)phenyl]-N-[6-(4-methylpiperazin-1-yl)-4-o-tolylpyridin-3-yl]-N-methylisobutyramide

Mode of Action: NEPA is a fixed combination of netupitant, a substance P/neurokinin 1 (NK) receptor antagonist, and palonosetron, a
serotonin-3 (5-HT) receptor antagonist

Description: NEPA (300mg netupitant/0.5mg palonosetron) capsules are hard gelatin capsules with white body and caramel cap with "HE1" printed on the body. Placebo for NEPA will be identical hard gelatin capsules with the "HE1" imprinted on the body.

How Supplied: Helsinn will supply NEPA and Placebo capsules to the site. The capsules are packaged as 1 capsule per blister pack/box.

Note: NEPA/Placebo may be repackaged from the supplied bottles and dispensed in pharmacy dispensing bottles according to the quantities specified by the investigator.

Storage: The recommended long term storage condition for NEPA/placebo capsules is USP controlled room temperature. Store at 20-25 °C (68-77 °F). Excursions permitted to 15-30 °C (59-86 °F).

Stability: NEPA/Placebo has a shelf-life of 4 years from date of manufacture.

Route(s) of Administration: Oral

Method of Administration: It is recommended patients should take NEPA (300mg netupitant/0.5mg palonosetron)/Placebo (1 capsule) orally with or without food.

Please refer to the NEPA package insert for safety profile and side effects/drug interactions.

Potential Drug Interactions: **CYP3A4 Interactions:**

- 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 Akynzeo. The inhibitory effect on CYP3A4 can last for multiple days. Patients on these medications will be monitored while on study.

Concomitant and Prohibited Medication

- Concomitant medications must be recorded in the electronic medical record from 28 days prior to the first dose of study drug through the last dose of study drug.
- The use of rescue medications will be allowed (metoclopramide 10 mg q4h PRN for breakthrough nausea).
- As specified within the Exclusion Criteria, scheduled strong or moderate CYP 3A4 inhibitors (boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole; amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil) are prohibited within one week of study enrollment. If a patient is required to take a strong CYP3A4 inhibitor while enrolled in this trial, they must be discontinued.
- As specified in the Exclusion Criteria, the administration of scheduled CYP3A4 substrates with narrow safety range at the time of study enrollment (alfentanil, cyclosporine, dihydroergotamine, ergotamine, pimozide, quinidine, sirolimus, tacrolimus) are prohibited. If a patient is required to take any of these drugs while enrolled in this trial, they must first be discontinued.

Drug Accountability:

Agent Ordering:

Helsinn will ship the medication to the Investigational Pharmacy Services. Drug re-ordering will be via a drug order form or electronic/fax communication with the Helsinn representatives.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, will maintain a record of the inventory and disposition of all agents received from Helsinn. Sites may use their own drug accountability logs per their standard procedures. Drug Accountability records will capture Lot numbers dispensed to the patient. Unused drug at the remainder of the trial and expired drug may be destroyed on site per the site's drug expiration policy or Helsinn will make arrangements for destruction.

Dose: Dose will be 300mg netupitant/0.5mg palonosetron. NEPA (300mg netupitant/0.5mg palonosetron)/Placebo capsules will be used in this study. No other capsule strengths are available and there are no permitted dose reduction schemes. Dosing may be delayed/interrupted at the discretion of the Investigator if needed due to an adverse event, and discussed with the patient.

D. Experimental Approach

D.1. Study Design. This is an investigator-initiated study supported by Helsinn**.** We propose a 2-arm, double blind, placebo run-in, parallel randomized controlled trial of NEPA vs. placebo for cancer patients with chronic nausea and vomiting, to be followed by an open label extension phase (Figure 1). This is a proof-of-concept study enrolling 30 evaluable patients. The main goal of this study is to determine the effect size for both NEPA and placebo arm in order to inform a larger, adequately powered confirmatory randomized controlled trial.

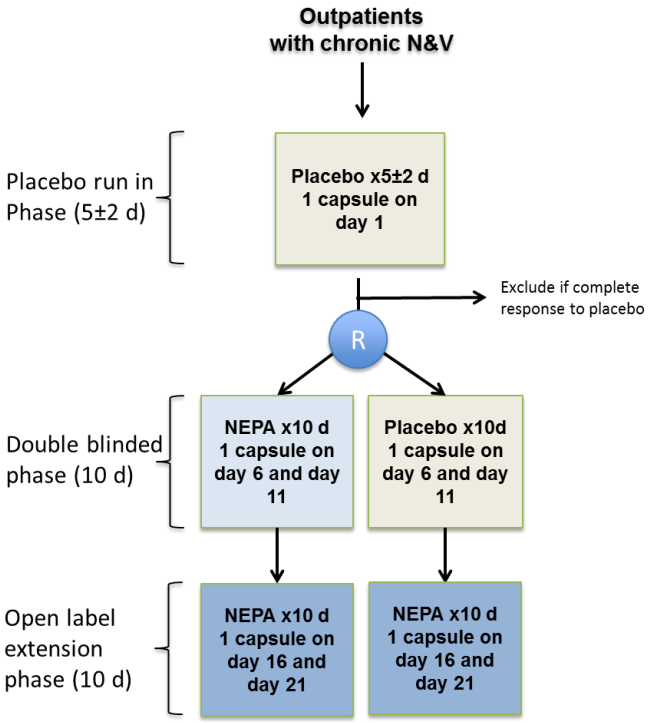

Figure 1. Study Design

After study consent, eligible patients will be asked to try a single dose of study medication (placebo) over a 5 +/-2 day period, in a single-blinded fashion. Those without a significant placebo response by Day 5 +/-2 will then be randomized to NEPA or placebo for 10 days. Study drug will be mailed to study participants. We will also offer an optional open label extension for 10 more days after the blinded phase so patients may receive NEPA for nausea control if desired. Patients will complete assessments similar to the blinded phase (Table 4). We believe this study design is feasible and would not add undue burden for patients. Patients will be compensated with a $50 gift card for their time and effort. Patients may also be reimbursed for parking charges for study visits at a total of up to $45 for all study visits.

The placebo run-in period will allow us to (1) evaluate patients prior to exposure to the experimental treatment, (2) exclude patients who develop a significant placebo response given that our primary outcome is subjective, and (3) select patients who have a higher chance of completing the study. This design has been used in multiple other supportive care randomized trials without affecting their internal validity.[33-35] The use of rescue medications will be allowed (metoclopramide 10 mg q4h PRN for breakthrough nausea).

D.2. Eligibility Criteria. The eligibility criteria are shown in Table 2.

Table 2. Study Eligibility Criteria

Inclusion Criteria

1. Diagnosis of cancer
2. Chronic nausea over the past 4 weeks
3. Average nausea numeric rating scale ≥4/10 over the past 5 days at screening
4. Outpatient at MD Anderson Cancer Center
5. Karnofsky performance status >/=50%
6. Age 18 or older
7. Able to complete study assessments, including keeping a daily diary

Exclusion Criteria

1. Delirium (i.e. Memorial Delirium Rating Scale >13)
2. Clinical evidence of bowel obstruction at the time of study enrollment
3. Expected to use other 5HT3 antagonists or NK1 antagonists for prophylaxis during the study
4. Continuation of over-the-counter therapies for nausea and/or vomiting during the study
5. On cytotoxic chemotherapy in the high/moderate/low emetogenic risk categories or oral antineoplastic agents in the high or moderate emetogenic risk categories according to the latest NCCN guideline within 2 weeks of study enrollment
6. On scheduled potent CYP3A4 inducers at the time of study enrollment (avasimibe, carbamazepine, phenytoin, rifampin, efavirenz, nevirapine, barbiturates, systemic glucocorticoids, modafinil, oxcarbazine, phenobarbital, pioglitazone, rifabutin, St. John's wort, troglitazone)[1]
7. On scheduled CYP3A4 substrates with narrow safety range at the time of study enrollment (alfentanil, cyclosporine, dihydroergotamine, ergotamine, pimozide, quinidine, sirolimus, tacrolimus)
8. On scheduled strong or moderate CYP3A4 inhibitors (boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole; amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil) within one week of study enrollment[1]
9. Unwilling to provide informed consent
10. Severe renal impairment (calculated Creatinine clearance <=29 cc/min)[2]
11. Severe liver impairment (Child-Pugh Score >9)[3]
12. Females who are pregnant, lactating, or intend to become pregnant during the participation of the study; childbearing age women who are not on birth control. Positive pregnancy test for women of childbearing potential, as defined by intact uterus and ovaries, and no history of menses within the last 12 months. Pregnancy test to be performed on the day of enrollment. In cases of women with elevated b-HCG, these candidates will be eligible to participate so long as the level of b-HCG is not consistent with pregnancy and the non-pregnant status is confirmed by a Gynecologic examination.

[1] according to FDA website http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

[2] Calculated creatinine clearance can be done within 14 days of study enrollment.

[3] T. bilirubin, albumin, prothrombin time, and serum creatinine tests can be done within 14 days of study enrollment (only if not performed in the last 14 days)

Birth Control Information
Taking part in this study can result in risks to an unborn or breastfeeding baby. Patients should not become pregnant, breastfeed a baby, or father a child while on this study. Sexually active patients must use birth control during the study.

Birth Control Specifications: Women who are able to become pregnant must use birth control during the study and for 30 days after the last NEPA dose.

Acceptable forms of birth control for men and women include barrier methods (such as condom or diaphragm) with spermicide, or abstinence.

Males must tell the doctor right away if their partner becomes pregnant or suspects pregnancy.

Pregnant women will not be enrolled on this study. If the patient becomes pregnant or suspects that she is pregnant, she must inform her doctor right away.
Pregnancy may result in removal from this study.

D.3. Study screening. A 2 step consent process will be used. First, a verbal consent will be obtained by the study staff to proceed with screening of potential participants for eligibility and to characterize their nausea and vomiting. Outpatients may be contacted by phone within 1 week prior to their scheduled clinic visit to inform them of this study so they can make necessary arrangements if interested in participating. Eligible patients will then be formally enrolled onto the study after they have signed the informed consent indicating a willingness to participate in the trial. The number of patients screened, approached, eligible, and enrolled will be documented. Reasons for refusal for eligible patients will also be captured.

D.4. Randomization. To be eligible for the blinded phase, individuals will need to have an average nausea NRS ≥ 4/10 prior to randomization on a day between day 3 and day 7 (i.e. day 5 +/-2). Patients who report a significant clinical response to placebo (i.e. NRS <4/10) during this time on the placebo run-in would not proceed to the double-blind phase and will be monitored until day 7 in case their nausea level increased again, in which case they will be eligible to proceed and will be randomized. Participants without significant clinical response to placebo will be randomized to either NEPA or placebo through the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct/DeskTopDefault.aspx) in a 2:1 ratio, and stratified by level of nausea NRS (average over past 24 hours, 4-6 vs 7-10) obtained prior to randomization.

D.5. Blinding. During placebo run-in, only the patient will be blinded and told that he/she will receive one of the two study treatments (Akynzeo or placebo). During the randomized phase, both the patient and the research staff conducting the assessment will be blinded to the treatment assignment. NEPA and identically appearing placebo will be dispensed by Dispensing Pharmacy at MD Anderson; only the pharmacy team will be aware of the identity of this study agent. Allocation concealment will be

maintained. We will check the blinding from patients and study staff at the end of study (Table 4).

Unblinding Procedures:
1. The Statistician and the investigational pharmacist will have access to the codes/assignments.
2. The codes will be revealed with prior approval from the DSMB and IRB only if there is a safety issue and the treating physician needs to be aware of the treatment assignment.
3. The PI should be contacted regarding and give approval for un-blinding
4. The Investigator/research team must inform the IND Office when un-blinding occurs.

D.6. Research staff. An orientation will be held with research staff involved in this study to introduce them with the study design and to standardize the provision of each intervention.

D.7. Study Interventions. The supply of study medication (both NEPA and placebo) will be provided by Helsinn. NEPA is a fixed dosed capsule consisting of 300 mg netupitant and 0.5 mg palonosetron. It was approved by the US Food and Drug Administration (NDA 205718) in October 2014 for "for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Oral palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy." During the double-blinded phase, patients will be asked to take NEPA or placebo orally on day 6 and on day 11 of the double-blind treatment period, and on day 16 and on day 21 of the open-label extension phase. Each dose lasts for 5 days. The capsule can be taken with or without food. The study medication will be stored below 30°C (86°F), not refrigerated, in a secure area with limited access and protected from light.

In the control arm, patients will be using metoclopramide on an as needed basis (see section D.8), which represents standard of care.

Previous studies of NEPA only used a single dose per cycle because CINV is mostly confined to the first 5 days. However, chronic nausea is present for longer periods of time thus one additional dose is proposed to alleviate nausea. Previous trials examining the use of NEPA for repeated cycles of chemotherapy (duration between cycles not specified) found that NEPA was well tolerated.[31] The most frequent NEPA-related side effects were constipation (3.6%) and headache (1%) and the investigators found no indication of increased adverse events over multiple cycles.[31] Thus, we propose to study NEPA with one repeat dose given the clinical need, its low side effect profile and the close monitoring of adverse events during this study.

D.8. Medication use during study. This information will be recorded in the patient diary. Patients will be allowed to use metoclopramide 10 mg PO on an as needed

basis. They will be asked not to take other anti-emetics (e.g. haloperidol, olanzapine, corticosteroids, antihistamines, anticholinergics) unless (1) they have already been using them on a scheduled basis for an indication other than nausea or (2) if metoclopramide is ineffective or intolerable, in which case they may use them as prescribed previously for rescue purposes. Metoclopramide will be provided free of charge to patients requiring rescue medication. All antiemetic medications during the study will be documented.

To minimize constipation, all patients will be advised to take a laxative regimen (e.g. senna 1-4 tablets BID, PEG 17 g PO BID PRN) prophylactically if they are on opioids and/or report any constipation symptoms.

D.9. Stopping rules. Patients who had a significant placebo response (see Section D.4) by day 4(+/-1) will not continue. Patients may also withdraw from study anytime and pursue standard of care. Patient dropouts prior to the administration of drug or placebo will be replaced.

D.10. Study assessments. See Table 4 for a detailed description of all study assessments.

Nausea numeric rating scale (primary outcome): To evaluate the efficacy of NEPA/placebo, each patient will complete a diary daily from time of enrollment through the end of study documenting the average intensity of nausea over the preceding 24 h and over the past 5 days at Baseline and on or about Days 5, 10, 15, 20, and 25 using a 0-10 NRS (where 0=no nausea and 10=worst possible. This scale has been used in multiple studies.[6,23] The primary efficacy endpoint is change in nausea intensity from day 5 to day 15. The minimal clinically important difference is 1 point.[36]

Secondary endpoints:

- Worst intensity of nausea—highest score over the preceding 24 h using a 0-10 NRS (where 0=no nausea and 10=worst possible).
- Number of doses of rescue antiemetic (i.e. metoclopramide) and total dose over the past 24 hours.
- Index of nausea and vomiting and retching (INV-R)—this validated questionnaire consists of 8 items asking about the patient's experience regarding nausea and vomiting over the past 12 hours. Each item includes a 5-point Likert scale (0-4 points) with descriptive words. The concurrent validity is 0.83-0.87, and Cronbach's alpha was 0.89-0.97.[37-39] The total score ranges from 0 to 32 points, with a higher score indicating more nausea/vomiting.
- Proportion of patients with complete response—defined as no significant nausea (average NRS≤2), no rescue medication for nausea/vomiting and no emesis. A vomiting episode is defined as a single vomiting episode (defined as expulsion of stomach contents), a single retching (defined as an effort to vomit without expulsion of stomach contents) or any retching combined with vomiting.[27-29,31]
- Global symptom evaluation – we will assess impression of change by asking them about their nausea and vomiting (worse, about the same, or better; If better, how

much better? Hardly any better, a little better, somewhat better, moderately better, a good deal better, a great deal better, a very great deal better; If worse, how much worse? Hardly any worse, a little worse, somewhat worse, moderately worse, a good deal worse, a great deal worse, a very great deal worse) comparing between the level of nausea and vomiting days 1-5 vs. days 6-15. Study satisfaction will be assessed with the following questions, "Was it worthwhile for you to participate in this research study?", "If you had to do it over, would you participate in this research study again?", "Would you recommend participating in this research study to others?", "Did your quality of life get better by participating in this research study?", "Did your quality of life get worse by participating in this research study?" Blinding will be assessed by asking patients and study staff which group assignment they believe they received: "NEPA", "placebo", or "do not know".

- Personalized Nausea Goal—we will assess personalized nausea goal by asking "At what level of intensity would you feel comfortable? 0-10 where 0=no nausea and 10=worst possible". Personalized nausea response is defined as nausea NRS ≤ personalized nausea goal. To assess stability of personalized nausea goal, we will be asking participants to provide this on day 15±2 as well.
- Functional Living Index Emesis (FLIE)—a questionnaire validated to assesses the impact of chemotherapy-induced nausea and vomiting on patient's function and quality of life over the past 5-days. It consists of 18 items, with 9 items on nausea and 9 items on vomiting. The questions include how much nausea/vomiting, and impact of these symptoms on recreation or leisure activities, make meal/do tasks, ability to enjoy meal, enjoy drinking fluids, see family/ friends, daily functioning, personal hardship, and hardship on others. Each question was rated using a numeric rating scale from 1-7. The total score range from 18 to 126, where a higher score indicates higher quality of life.[43-46]

D.11 Feasibility data. In addition to clinical outcomes, we will also collect feasibility data in this study, including the following:

- Rates of recruitment and retention (% of subjects able to complete the study)
- Reasons for refusal and dropout
- Participant satisfaction—participants will provide an opinion regarding their satisfaction with study overall

D.12. Patient Safety, Monitoring, and Confidentiality. Regulatory monitoring will be provided by the principal investigator, Institutional Review Board (IRB), and the Data Safety Monitoring Board (DSMB). Patient confidentiality will be ensured by use of study numbers, secure storage of clinical data, and anonymous reporting.

Table 4. Summary of Study Assessments

Assessments	Day of enrollment	Days 1-25	Day 5±2	Day 10±2	Day 15±2	Days 20±2 25±2[1]
Screening procedures (eligibility criteria)/ Pregnancy Test/Calculated creatinine clearance, T. bilirubin, albumin, prothrombin time, serum creatinine	✓ Pregnancy test within 7 days of					

	signing consent				
Baseline characteristics[2] (Appendix A)	✓				
Medication history[3] (Appendix A)	✓				
Nausea Diary including nausea numeric rating scale (primary outcome), rescue medications and Index of nausea and vomiting and retching[4] (Appendix B)		✓*			
Edmonton Symptom Assessment Scale[5] (Appendix C)	✓		✓*	✓*	✓*
Personalized nausea goal[6] (Appendix D)	✓			✓*	
Functional Living Index Emesis[7] (Appendix E)	✓		✓*	✓*	✓*
Global assessment (Appendix F), study satisfaction (Appendix H) and blinding (Appendix G)[8]				✓*	
Nausea Numeric Rating Scale past 5 days (Appendix U)[9]	✓	✓*	✓*	✓*	✓*

* Assessments may be done over the phone or in person from day 1 to day 15±2, and on day 20±2 and 25±2. For the other days starting day 16 (open label phase), patients will continue to complete assessments in the diary on their own until the end of study.

[1] Optional extension phase

[2] patient initials, medical record number, date of birth, sex, race, education, marital status, cancer diagnosis, stage, co-morbidities, cause(s) of nausea, date of last cancer treatment, Karnofsky Performance status, Memorial Delirium Assessment Scale (MDAS).[41]

[3] all scheduled and as needed medications that could be used to treat nausea, such as metoclopramide, haloperidol, olanzapine, corticosteroids, 5HT3 antagonists, antihistamines, anticholinergics will be documented.

[4] To evaluate the efficacy of NEPA/placebo, each patient will complete a diary from time of enrollment through the end of study documenting the average intensity of nausea over the preceding 24 h using a 0-10 NRS (where 0=no nausea and 10=worst possible), the worst intensity of nausea over the preceding 24 h using the same 0-10 NRS (where 0=no nausea and 10=worst possible), the number of doses of rescue antiemetic (i.e. metoclopramide) and total dose over the past 24 hours, and the Index of nausea and vomiting and retching (see Section D.10).

[5] validated questionnaire that measures 9 other common symptoms in the past 24 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well-being) using numeric rating scales.[42]

[6] we will assess personalized nausea goal by asking "At what level of intensity would you feel comfortable? 0-10 where 0=no nausea and 10=worst possible" [40]. Personalized nausea response is defined as nausea NRS ≤ personalized nausea goal. To assess stability of personalized nausea goal, we will be asking participants to provide this on day 15±2 as well.

[7] Functional Living Index Emesis (FLIE) is a questionnaire validated to assess the impact of chemotherapy-induced nausea and vomiting on patient's function and quality of life over the past 5-days. It consists of 18 items, with 9 items on nausea and 9 items on vomiting. The questions include how much nausea/vomiting, and impact of these symptoms on recreation or leisure activities, make meal/do tasks, ability to enjoy meal, enjoy drinking fluids, see family/ friends, daily functioning, personal hardship, and hardship on others. Each question was rated using a numeric rating scale from 1-7. The total score range from 18 to 126, where a higher score indicates higher quality of life.[43-46]

[8] Patient Global Impression of Change will be assessed by asking them about their nausea and vomiting (worse, about the same, or better; If better, how much better? Hardly any better, a little better, somewhat better, moderately better, a good deal better, a great deal better, a very great deal better; If worse, how much worse? Hardly any worse, a little worse, somewhat worse, moderately worse, a good deal worse, a great deal worse, a very great deal worse) comparing

between the level of nausea and vomiting days 1-5 vs. days 6-15.[47,48] Study satisfaction will be assessed with the following questions, "Was it worthwhile for you to participate in this research study?", "If you had to do it over, would you participate in this research study again?", "Would you recommend participating in this research study to others?", "Did your quality of life get better by participating in this research study?", "Did your quality of life get worse by participating in this research study?" Blinding will be assessed by asking patients and study staff which group assignment they believe they received: "NEPA", "placebo", or "do not know".

[9] Average nausea NRS over the past 5 days at baseline and on days 5±2, 10±2, 15±2, 20±2, and 25±2

D.13.Source Documentation. The medical record and questionnaire responses will be considered source data.

The Investigator or physician designee is responsible for providing source documentation and assigning attribution for all AEs.

D.14. Subject Compliance. Site personnel will assess treatment compliance at each visit during the treatment period using the patient's diary and by the patient returning the unused study medication and/or empty study medication bottle.

E. Patient Withdrawal Criteria

Patients may withdraw their consent at any time and discontinue the study. Patients may also be discontinued from the study at any time for the following reasons:

- Adverse event requiring cessation of study drug (adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug)
- Major protocol violation (patient lost to follow-up, hospitalization resulting from major side effects, lack of consent, lack of safety laboratory tests)
- Lost to follow-up (We will make every effort to follow all randomized patients including contact of family members and/or other medical facilities to avoid losing patients to study follow-up)
- Death
- For patients who experience an adverse event requiring cessation of study drug, they will be followed until the event resolves, until they begin another clinical trial, or until the end of the study. However, certain adverse events (e.g., a cerebrovascular accident, worsening hypertension) will not be expected to resolve completely; in these cases, the date and time should be recorded when the event reaches its new, stable equilibrium and any remaining residual of the event should be documented.
- Suspected pregnancy
- We will add replacement patients to account for withdrawals until we reach 30 total patients.

Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

- Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section F below

- Intensity
  The intensity of the AE is classified according to the CTCAEv4.0. Grade refers to the severity (intensity) of the AE:

  CTCAEv4 Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

  CTCAEv4 Grade 2: moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).

  CTCAEv4 Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self care ADL (self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

  CTCAEv4 Grade 4: life-threatening consequences; urgent intervention is indicated.

  CTCAEv4 Grade 5: death due to an AE.

Expected adverse events such as headache, fatigue, nausea, diarrhea, and AEs assessed as Grades 1 and 2 will not require reporting to Helsinn. Adverse events will be tracked and submitted during annual review to the IRB. Adverse events (including event name, grade, start/stop date and attribution) will be entered into Prometheus. The Principal Investigator or physician designee will verify the attribution assigned in Prometheus by signing the Prometheus adverse events printout at the end of protocol treatment. Prometheus will be utilized as the electronic case report form for this study.

Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information.

The causality assessment should be done separately for each study treatment.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”. An assessment of “no” would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

F. Investigator Communications with Helsinn

As stipulated in 2.6 of the Strategic Collaboration Agreement, MD Anderson is the sponsor and assumes all obligations regarding the preparation and submission of individual and aggregate safety reports to FDA, Ethic Committee, and other relevant persons to the extent required by and as per the applicable US laws, regulations, and guidelines. The Principal Investigator will forward to Helsinn any serious adverse reaction (i.e. for which it is judged there is a reasonable causal relationship between the study drug and the adverse event) on the MedWatch Form, regardless of its expectedness, within 24 hours from first awareness, including follow-ups.

The Principal Investigator shall provide Helsinn with relevant safety data including study and IND safety reports (prior to their finalization) and any safety signal or risk (with the rationale) originating from the study. The e-mail address for exchanging all the above mentioned safety information is: drug-safety@helsinn.com.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I	Phase I	Phase I	Phase I	Phase I

	Phase II	Phase II Phase III	Phase II Phase III	Phase II Phase III	Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Adverse events will be captured according to the recommended AE recording guidelines for a Phase II protocol.

G. Serious Adverse Event Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

H. Statistical Considerations

The primary objective of this phase II study is to estimate the effect of NEPA on the nausea numeric rating scale (i.e. change between day 5 and day 15). The target accrual is 30 evaluable patients who complete the study with a randomization ratio of 2:1 (NEPA vs Placebo), but accrual will range from 41-50, given an attrition rate of 30-40%. With 20 patients in the NEPA arm, we would have a 92% power to detect a difference of 2 points with a standard deviation of 2.5 (effect size of 0.8) using two-sided paired t-test with a significance level of 0.05.

Descriptive statistics, including mean, standard deviation, 95% confidence intervals, median, range, frequency and percentage will be summarized for all variables of interest such as patients' demographics, clinical characteristics, personalized nausea goal, NRS and adverse effects, whichever appropriate.

We will focus on estimating the magnitude of change in NRS between day 5 and day 15. We will use a mixed model to examine the change in nausea overtime in both the NEPA arm and placebo arm.

We will estimate the proportion (with 95% confidence interval) of patients who achieve their personalized nausea goal for NEPA and placebo as a secondary outcome. Adverse effects associated with NEPA and placebo will be collected and frequency will be summarized.

A comparison between NEPA and placebo is not the objective of this study. However, Chi-squared test or Fisher's exact test, whichever the most appropriate, will be used to test for association between categorical variables, such as CTCAE adverse effects, global assessment, and blinding. Wilcoxon rank sum test or Kruskal-Wallis test will be used to test for difference of continuous variables, such as ESAS and FLIE. General

linear model may be considered to examine the effect of potential important factors on NRS.

A Response/Toxicity Summary will be submitted to the IND Office Medical Monitor, after the first ten evaluable patients complete study treatment, and every 10 evaluable patients thereafter.

I. Data Confidentiality Procedures

This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

During the study, trained research staff will be performing study assessments and monitoring the patient carefully throughout the study period. Regulatory monitoring will be provided by the principal investigator and the IND office. Patient confidentiality will be maintained by use of unique study numbers, secure storage of clinical data, and anonymous reporting.

Collection of identifiers: We will collect and securely store patients' identifiers (including name and medical record number). Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Protection of electronic and paper records will be maintained to the best of our ability. All electronic records will be stored on password-protected institution computers behind the institution firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principal investigators, co-investigators, and the research team will have access to study records.

Data sharing: Study data will not be shared with any individuals or entities outside of the MD Anderson Research Group and Supporter without an IRB-approved protocol. The data will be kept by the principal investigator in a locked file cabinet and password-protected database.

Final disposition of study records: These data will be used only for this research study. Entities outside of the MD Anderson Research Group and Supporter will not be allowed access to the data without an IRB-approved protocol. PHI may be maintained indefinitely, aggregated in the future, and used for future research studies.

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