Efficacy and Safety of Phosphorolapipatim Palonosetron for Preventing Nausea and Vomiting Caused by Multi-cycle Immunotherapy + Chemotherapy in Patients with Esophageal Cancer and Lung Cancer

Version: 2.2

Version date: May 14,2026

Solution Signature Page

Sponsor's signature

I will conscientiously fulfill the responsibilities of sponsor and investigator in accordance with China GCP regulations, personally participate in or directly supervise this clinical study. Our party has read and confirmed this protocol (Version No.: 2.1, Version Date: January 14,2026). I agree to perform relevant duties in compliance with Chinese laws, the Declaration of Helsinki, China GCP, any applicable laws and regulations, and this study protocol. I confirm that the protocol or revised protocol will only be implemented after obtaining approval from the ethics committee, unless measures are necessary to protect the safety, rights, and interests of subjects.

Research institution: The Second Affiliated Hospital of Zhejiang University School of Medicine

_____

Principal Investigator (bold) Principal Investigator (signature) Date of signature (year/month/day)

scenario summary

Research Title	Efficacy and Safety of Phosphorolapipatim Palonosetron for Preventing Nausea and Vomiting Caused by Multi-cycle Immunotherapy + Chemotherapy in Patients with Esophageal Cancer and Lung Cancer
Version number and date	Version 2.2, May 14,2026
Drug Name	Phosphorolapiptan Palonosetron for Injection
Principal Investigator	Professor Shen Hong
Research Participation Center	Approximately 5 centers
purpose of research	Evaluation of the efficacy and safety of fosfoprazanilide palonosetron for injection in preventing nausea and vomiting induced by multiple cycles of immunotherapy plus chemotherapy in patients with esophageal cancer and lung cancer
study population	The plan involves esophageal cancer and lung cancer patients who will receive platinum-based immunotherapy plus chemotherapy regimens for at least 4 cycles.
research design	This study adopted a randomized, parallel, cohort design. Based on data from previous Phase III studies, the super-delayed complete response (CR) rate for HR20013+ dexamethasone in the first cycle to prevent nausea and vomiting induced by highly emetogenic chemotherapy was 90.3%, while the CR rate for fosapitant + dexamethasone + palonosetron was 86.5%. With a planned enrollment of 57 subjects per group, the 95% confidence interval (CI) width for the CR rates in both groups could be maintained within 0.2. Considering a 5% dropout rate, 60 subjects were enrolled in each group. The trial consists of three phases: screening, treatment, and safety follow-up. Eligible participants receive pharmacotherapy as specified in the trial protocol, followed by corresponding follow-up visits and examinations according to the trial schedule. During the study period, if investigators determine that participants require rescue antiemetic medication, such treatment may be administered based on clinical needs. The specific types of medications, administration methods, dosages, and frequency are determined by the investigators.
Administration route	**Queue 1:** • Phosphorotapiratam Palonosetron for Injection: Administered via intravenous infusion for 1 hour (+10 minutes), once before each chemotherapy cycle. • Dexamethasone acetate: Oral administration of 12 mg on the first day of each chemotherapy cycle prior to chemotherapy, followed by 3.75 mg twice daily (bid) on days 2-4. **Queue 2:**

	• Fosapiritan and Nifedipine for Injection: 150 mg, administered via intravenous infusion over 20-30 minutes, once before each chemotherapy cycle. • Palonosetron hydrochloride: 0.25 mg, administered via intravenous push infusion for at least 30 seconds, once before each cycle of chemotherapy. • Dexamethasone acetate: Oral administration of 6 mg on the first day of each chemotherapy cycle prior to chemotherapy, 3.75 mg once on the second day, and 3.75 mg twice daily (bid) on days 3-4.
Admission criteria	(1) Age ≥18 years, with no gender restriction; (2) Locally advanced/metastatic esophageal cancer and lung cancer confirmed by histology or cytology, and treated as first-line therapy; (3) Planned to receive at least 4 cycles of chemotherapy based on cisplatin and carboplatin combined with immunotherapy; (4) Expected survival duration ≥3 months; (5) Eastern Cooperative Oncology Group (ECOG) physical status score of 0 or 1; (6) Good organ function, meeting the following criteria: a: Neutrophil count ≥1.5×10^9/L; b: Hemoglobin ≥ 90 g/L; c: Platelet count ≥ 100×10^9/L; d: Total bilirubin ≤1.5×ULN; e: In patients without known liver metastases, aspartate aminotransferase (AST) ≤ 2.5×ULN and/or alanine aminotransferase (ALT) ≤2.5×ULN (for patients with liver metastases, the limit may be relaxed to ≤5×ULN); f: Serum creatinine ≤1.5×ULN or creatinine clearance rate ≥50 ml/min; g: Electrocardiogram (ECG): QTc ≤450 ms (male), QTc ≤470 ms (female); h: Echocardiography: LVEF (left ventricular ejection fraction) ≥50%; (7) Female participants of reproductive age, as well as male participants whose partners are women of reproductive age, must have employed an effective contraceptive measure from the time of signing the informed consent form until 6 months after the last dose administration. Female participants of reproductive age must have a negative blood pregnancy test result within 72 hours prior to randomization and must not be in the lactation period. (8) Clearly understand and voluntarily participate in this study, and sign the informed

	consent form personally.
Exclusion criteria	(1) Received or planned to receive abdominal (including diaphragmatic plane and below) or pelvic radiotherapy within the previous 7 days prior to randomization, or during days 1 to 8 of treatment; (2) Administration of chemotherapy agents with high emetogenic risk is planned within days 2 to 8 after platinum infusion; (3) Planned to receive chemotherapy regimens including conventional paclitaxel (using castor oil as solvent); (4) Randomly administer drugs with potential antiemetic effects within the preceding 2 days: first-generation 5-HT3 receptor antagonists (e.g., ondansetron), phenothiazines (e.g., prochlorazine), butyrophenones (e.g., haloperidol), benzamide derivatives (e.g., metoclopramide), domperidone, cannabinols, traditional Chinese medicines with potential antiemetic effects, scopolamine, and cecirizine. (5) Had started treatment with benzodiazepines or opioid preparations within the preceding 2 days (excluding triazolam, temazepam, or midazolam taken alone daily); (6) Subjects who began morphine use within the preceding 7 days (excluding those on stable dosage regimens); (7) Received systemic corticosteroid therapy (including but not limited to dexamethasone, hydrocortisone, methylprednisolone, or prednisolone) or sedative antihistamines (such as diphenhydramine) within the preceding 7 days (Note: Single-dose steroid administration for contrast agent allergy prophylaxis and topical or inhaled administration are permitted), except for cases requiring hormone pretreatment on the day before chemotherapy. (8) Palonosetron use within the preceding 14 days; (9) Use of NK-1 receptor antagonists within the preceding 28 days; (10) Use of specific CYP3A4 substrates (terfenadine, cisapride, astemizole) or CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, ketoconazole or itraconazole, diltiazem) within 7 days prior to randomization, or use of strong CYP3A4 inducers (e.g., phenobarbital, rifampin, phenytoin, carbamazepine) or specific CYP2D6 substrates (thiuridazine, pimozide) within 28 days prior to randomization; (11) Vomiting and/or retching, nausea occurring within the preceding 24 hours; (12) Subjects with symptomatic brain metastases; (13) Accompanied by poorly controlled serous cavity effusions, including pleural effusion, ascites, and pericardial effusion (patients with controlled effusions stabilized

	for ≥2 weeks after treatment may be included); (14) History of severe cardiovascular disease within the preceding 3 months, including but not limited to acute myocardial infarction (AMI), unstable angina pectoris, significant valvular or pericardial disease, history of ventricular tachycardia, symptomatic chronic heart failure (New York Heart Association [NYHA] class II to IV), and history of severe cardiac conduction abnormalities (e.g., torsades de pointes). (15) Randomized prior coexisting poorly controlled hypertension (two consecutive resting systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg); (16) Patients with concurrent active hepatitis B virus infection (HBV DNA ≥ 2000 IU/mL or 104 copies/mL), active hepatitis C virus infection (HCV-Ab positive with HCV-RNA ≥ upper limit of normal), acquired immunodeficiency syndrome (AIDS) or positive HIV test results, or positive syphilis test results; (17) Concomitant diseases contraindicated for dexamethasone administration, such as active infections (e.g., pneumonia) or any uncontrolled conditions (e.g., diabetic ketoacidosis, gastrointestinal obstruction, etc.); (18) Known contraindications for NK-1 receptor antagonists, 5-HT3 receptor antagonists, or dexamethasone; (19) Participation in other clinical trials within the preceding 30 days (based on the use of investigational drugs); (20) Subjects deemed by investigators to have other conditions unsuitable for participation in this study.
Criteria for discontinuation of study treatment	Participants have the right to terminate study treatment at any time for any reason. Reasons for terminating study treatment by participants include but are not limited to: (1) The subject requested to terminate continued treatment; (2) Occurrence of pregnancy events in subjects during the study process; (3) Situations where the investigator deems it necessary for the subject to discontinue treatment: a. Occurrence of any adverse event, abnormal laboratory findings, or other medical conditions that may result in continued medication use no longer being beneficial for the subject, or pose significant risks to health or safety; b. Discovery of more severe protocol violations renders the participant unsuitable for continued trial participation; c. Other circumstances in which continuing the trial would significantly affect the health or safety of the subjects.

Exit study criteria	(1) The subject voluntarily withdrew and refused further follow-up; (2) Loss to follow-up; (3) Death; (4) Early termination of the study by the sponsor.
Effectiveness Evaluation	**Primary endpoint** • The proportion of subjects achieving complete remission (CR: no vomiting and no rescue therapy) during the hyperdelayed period (120 h-168 h) after chemotherapy initiation in each immunotherapy plus chemotherapy cycle; **secondary endpoint** • The CR rates during the acute phase (0-24 h), delayed phase (24 h-120 h), overall phase (0-120 h), and 0-168 h periods of each immunotherapy plus chemotherapy cycle; • The time to first vomiting was also compared using Kaplan-Meier curves. • The Functional Life Index-Vomiting (FLIE) was used to assess the impact of chemotherapy-induced nausea and vomiting (CINV) on quality of life.
safety evaluation	The incidence rates of adverse events and serious adverse reactions during the entire study period, such as safety concerns including prolonged Q-T interval and constipation.
Sample size	This study adopted a randomized, parallel, cohort design. Based on data from previous Phase III studies, the super-delayed complete response (CR) rate for HR20013+ dexamethasone in the first cycle for preventing nausea and vomiting induced by highly emetogenic chemotherapy was 90.3%, while the CR rate for fosapitant + dexamethasone + palonosetron was 86.5%. With a planned enrollment of 57 subjects per group, the 95% confidence interval (CI) width for the CR rates in both groups could be maintained within 0.2. Considering a 5% dropout rate, a total of 60 subjects were enrolled per group, resulting in a total of 120 subjects.
statistical analysis	**Population analysis** Full Analysis Set (FAS): Includes all enrolled subjects who received the investigational drug, with primary efficacy analysis based on FAS. Safety Analysis Set (SS): Includes all enrolled subjects who received at least one dose of the study drug. **Efficacy Analysis** If a participant's assessment of vomiting episodes is missing on any day during the overall period, resulting in an inability to determine whether the participant has achieved complete remission, the participant is recorded as having incomplete

	remission. Sensitivity analysis for primary estimation targets: The sensitivity analysis methodology is identical to that of the primary estimation method, with only differences in the missing value imputation rules. If a participant's assessment of vomiting episodes is missing on any day during the study period, complete remission is determined based on the available data from that participant. If the subject's assessment of vomiting episodes is missing on any day within the extended delay period, resulting in an inability to determine whether the subject has achieved complete remission, the subject is recorded as having incomplete remission. **safety analysis** AEs will be coded using the MedDRA dictionary. The frequency and incidence of treatment-emergent adverse events (TEAEs) will be summarized by grouping according to System Organ Classification (SOC), preferred terms, and severity. Outcomes such as vital signs, electrocardiogram (ECG), and other clinical laboratory tests will be summarized by relative changes from baseline. Additionally, abnormal clinical laboratory test results will be described in a separate table.
Mid-term analysis	This study plans to conduct an interim analysis when 40% of participants have completed the study, utilizing the O'Brien & Fleming consumption function to determine non-binding invalid thresholds. The interim analysis will include non-blind key efficacy data and safety data, to be performed by an independent statistical analysis team. An Independent Data Monitoring Committee (IDMC) will review the interim analysis results and provide recommendations to the sponsor.

catalogue

1 Research Background

1.1 Background

Anticancer drug-induced nausea/vomiting is referred to as chemotherapy-induced nausea/vomiting (CINV) [1]. Approximately 60-80% of patients experience CINV [2], which is a challenging adverse reaction to anticancer drugs. CINV can lead to metabolic disturbances, deterioration of self-care ability and functional status, nutrient depletion, loss of appetite, decline in physical and mental state, as well as potential complications such as wound dehiscence and esophageal laceration. In severe cases, it may even result in patients discontinuing potentially effective or curative anticancer treatment regimens [1]. CINV occurs during the acute phase (symptoms appearing within 24 hours after chemotherapy) and the delayed phase (lasting up to five days) [3].

Chemotherapeutic agents can activate neurotransmitter receptors in the posterior limb of the brain or stimulate the afferent nerves of the vagus nerve near intestinal enterochromaffin cells [4]. Within 24 hours after chemotherapy initiation, the oxidative effects of free radicals generated by chemotherapeutic agents activate peripheral pathways, while these agents stimulate enterochromaffin cells in the gastrointestinal tract to release serotonin. Serotonin subsequently activates abdominal afferent vagus nerve fibers as part of the peripheral vomiting pathway and triggers emesis through the vomiting chemical compound (VC) [5]. Therefore, activation of peripheral pathways is primarily associated with acute chemotherapy-induced nausea and vomiting (CINV) [4]. Chemotherapeutic agents can also induce substance P release in both central and peripheral nervous systems, leading to NK-1-mediated vomiting [5]. Most studies indicate that central NK-1 receptors, particularly those expressed in the nucleus tractus solitarii (NTS) and posterior limb of the brain, mediate nausea induced by chemotherapy-induced substance P release [6-7]. Clinical trial results with 5-HT3 and NK-1 receptor antagonists further support the central NK-1 activation as a key factor in delayed CINV onset [8].

With the increasing complexity and efficacy of chemotherapy regimens, effective antiemetic strategies have become increasingly critical, particularly for patients receiving moderately or highly emetogenic chemotherapy (MEC and HEC). To date, combination chemotherapy containing cisplatin or other platinum compounds remains the first-line treatment for various malignancies (including lung cancer, ovarian cancer, cervical cancer, breast cancer, and bladder cancer) [9-14]. However, severe side effects associated with cisplatin often lead to significant deterioration in patients' quality of life and may result in dose reduction or chemotherapy discontinuation. One of the most common adverse effects of cisplatin is chemotherapy-induced nausea and vomiting (CINV), with an incidence rate approaching 90% in patients receiving high-dose cisplatin without antiemetic therapy [15]. A Phase II study [16] demonstrated that the NEPA regimen (naltopide + palonosetron) maintained its high antiemetic efficacy observed in the first cycle across multiple AC (anthracycline and cyclophosphamide) chemotherapy cycles in breast cancer patients. Preliminary evidence suggests that achieving complete response (CR)

throughout the treatment course also influences the risk of delayed-onset CINV during each AC chemotherapy cycle. In studies evaluating the addition of oral NK1 antagonists to standard antiemetics for cisplatin-based multi-cycle chemotherapy to prevent nausea and vomiting [17],64% of patients in the NK1 group achieved complete response in the first cycle compared to 49% in the standard treatment group. Subsequently, the complete response rate remained at 59% in the NK1 group by cycle 6, whereas it declined to 34% in the standard treatment group by cycle 6.

Currently, commonly used antiemetic drugs in clinical practice can be broadly classified into 5-HT3 receptor antagonists, NK-1 receptor antagonists, glucocorticoids, atypical antipsychotics, benzodiazepines, phenothiazines, and other types of antiemetics based on their mechanisms of action. The "China Expert Consensus on Prevention and Treatment of Nausea and Vomiting Related to Oncology Drug Therapy" (2019 edition) and the "China Society of Clinical Oncology (CSCO) Guidelines for Prevention and Treatment of Nausea and Vomiting Related to Antineoplastic Therapy" [18] (2019) both recommend the use of a triple-drug regimen prior to chemotherapy to prevent nausea and vomiting caused by highly emetogenic chemotherapy regimens, with a preferred combination of 5-HT3 receptor antagonists, dexamethasone, and NK-1 receptor antagonists (Class 1 evidence).

Phosphorotaparin Palonosetron for Injection is a combination preparation of NK-1 receptor antagonist and 5-HT3 receptor antagonist, used to prevent nausea and vomiting induced by highly emetogenic chemotherapy regimens. The prodrug of rotaparin is rapidly converted to active rotaparin after administration. Rotaparin is a highly selective NK-1 receptor antagonist with no significant affinity for NK-2 or NK-3 receptors, other receptors, transporters, enzymes, or ion channels. Palonosetron is a second-generation 5-HT3 receptor antagonist. Compared to first-generation 5-HT3 receptor antagonists (ondansetron, grasetron, dorzagliptin, etc.), palonosetron exhibits higher receptor affinity, longer half-life (approximately 40 hours, 4 to 10 times that of ondansetron, grasetron, and dorzagliptin), and favorable safety profile. In the Phase III trial of Phosphorotaparin Palonosetron for Injection [19], all patients received two cycles of HEC therapy, namely a cisplatin-based single-dose chemotherapy regimen (cisplatin dose ≥ 60 mg/m ^{2}, IV, D1, Q3W). The efficacy of Phosphorotaparin Palonosetron for Injection + DEX in preventing nausea and vomiting was noninferior to that of FAPR+PALO+DEX, with excellent safety profile. Additionally, the study found that Phosphorotaparin Palonosetron for Injection + DEX may enhance clinical benefits during the superdelayed period. Compared with FAPR+PALO+DEX, fosfoprazanopatil palonosetron injection + DEX demonstrated potential for improving quality of life in patients receiving HEC chemotherapy, particularly during the delayed and super-delayed phases.

Phenylpropanolat palonosetron, a combination of NK-1 receptor antagonist and 5-HT3 receptor antagonist, represents a novel fixed-dose intravenous antiemetic agent that

simultaneously antagonizes neuropeptide-1 and serotonin-3 receptors. Given that cancer patients typically undergo multiple cycles of chemotherapy, this prospective study was conducted to evaluate whether the antiemetic efficacy of phenylpropanolat palonosetron would be maintained in subsequent chemotherapy cycles.

1.2 Preclinical studies of pralopiratam and palonosquen

1.2.1 Major Pharmacodynamic Studies

Given that the pharmacological effects of rolapitamab and palonosetron have been extensively studied and validated in preclinical and clinical trials, phosphorolapitamab palonosetron was primarily evaluated for its in vitro activity against NK-1/NK-2/NK-3 receptors using the rolapitamab prodrug HRS5580. The antagonistic activity of HRS5580 against these receptors was tested using HEK-293 cell lines stably expressing NK-1, NK-2, or NK-3 receptors. After incubating HRS5580 or positive controls with the corresponding cells for 30 minutes, the appropriate receptor agonists (substance P, Neurokinin A, or Neurokinin B TFA) were added, and intracellular calcium flux intensity was recorded to reflect the antagonistic effect of HRS5580 on the respective receptors. The results demonstrated that the rolapitamab prodrug HRS5580 exhibited no antagonistic activity against NK-1, NK-2, or NK-3 receptors in vitro.

1.2.2 Secondary Pharmacodynamic Studies

Using a screening model established for safety evaluation, the study investigated the effects of HRS5580 on 42 early-stage drug safety targets. Safety assessment was conducted by evaluating the agonistic or inhibitory effects of HRS5580 on targets through functional activity screening methods. Results demonstrated that at a concentration of 10 μM, HRS5580 exhibited no significant agonistic or inhibitory effects on all 42 targets, with both agonism and inhibition rates remaining below 50%. These findings indicate relatively low off-target safety risks.

1.2.3 Pharmacokinetic Studies

1.2.3.1 Pharmacokinetic study of single intravenous injection of pralopiratam and palonosetron in rhesus monkeys

After intravenous administration of HRS5580 to rhesus monkeys, the parent drug HRS5580 rapidly converts to its active metabolite rolapitamab in plasma. HRS5580 is eliminated from plasma quickly with a half-life of only 0.16 hours, and no detectable parent drug remains in plasma 2 hours post-donation, with rolapitamab being the predominant metabolite. The parent drug exposure is approximately equivalent to 1.7% of rolapitamab. Following HRS5580 administration, plasma rolapitamab exposure levels approach those observed after equivalent molar doses of rolapitamab hydrochloride, with an AUC ratio of 98.9%. After intravenous administration of fosforolapitamab palonosetron to rhesus monkeys, HRS5580 rapidly converts to rolapitamab in plasma, with a half-life of only 0.13 hours. HRS5580 is undetectable in plasma 2 hours post-donation, and its AUC is approximately equivalent to 2% of rolapitamab. Plasma exposures of HRS5580 and rolapitamab were 115% and 100.2% of those observed in the HRS5580-treated group, respectively.

The plasma exposure of rolapipitan was 99.1% of that of the isomolar dose of rolapipitan hydrochloride injectable emulsion. Following a single intravenous injection of fosforylated rolapipitan palonosetron, the plasma exposure of palonosetron was 80.7% of that observed with a single dose of palonosetron monotherapy.

1.2.3.2 Study on tissue distribution of single intravenous injection of HRS5580 in SD rats

After a single intravenous injection of 20 mg/kg HRS5580 in SD rats, only low concentrations of the parent drug were detected in tissues collected at 10 minutes post-administration. The majority of tissues exhibited concentrations below 1% of plasma levels, with rolapitamab being the predominant drug in tissues. Ropalitamab was primarily distributed in the lungs, adrenal glands, liver, pancreas, ovaries, adipose tissue, kidneys, spleen, and heart, with tissue concentrations consistently exceeding plasma levels and tissue exposure exceeding plasma exposure by approximately 10-fold. Brain tissue exposure was approximately 4.7 times higher than plasma exposure, indicating its ability to cross the blood-brain barrier. The concentration ratio of rolapitamab in whole blood to plasma was 0.95, suggesting its entry into red blood cells. Tissue exposure of rolapitamab in female rats was approximately three times that observed in male rats. At equivalent molar doses, intravenous administration of HRS5580 in rats resulted in rolapitamab exposure levels in most tissues comparable to those observed after emulsion administration, with exposure ratio values ranging from 0.73 to 1.33.

1.2.3.3 Metabolic study of HRS5580 in an in vitro hepatocyte system

After incubation for 180 minutes in various hepatocyte metabolic systems, HRS5580 primarily undergoes amide hydrolysis metabolism to generate rolapitamab. The metabolic rate of HRS5580 is highly consistent across different hepatocyte species, with no significant interspecies differences observed. The metabolism of HRS5580 is mainly catalyzed by cytoplasmic enzymes containing free sulfhydryl groups and microsomal hydrolytic enzymes, with carboxylic esterases CES1 and CES2 playing a minor role in hydrolysis.

1.2.3.4 Metabolite Study of HRS5580 in Animals

HRS5580 undergoes extensive metabolism in rats, with 27 metabolites detected. The primary metabolic pathways include hydrolysis to form rolapipitan (M1), followed by further metabolic processes such as mono-oxidation (M2), dehydrogenation (M3), mono-oxidation coupled dehydrogenation (M4), and dual oxidation coupled dehydrogenation (M5), with the majority excreted via feces. In both rat and rhesus monkey plasma, the predominant metabolite is the hydrolyzed rolapipitan. Only trace amounts of the parent drug HRS5580 were detected in pooled blood samples collected within 2 hours after intravenous administration, while no HRS5580 was detected in urine or fecal samples.

2 Research Objectives

To evaluate the efficacy and safety of fosfoprolaplatin palonosetron for injection in preventing nausea and vomiting induced by multiple cycles of immunotherapy plus chemotherapy

in patients with esophageal cancer and lung cancer.

3 Study Design and Methods

This study is a randomized, parallel, cohort study designed to enroll 120 subjects, with 60 subjects per cohort. An interim analysis will be conducted when 40% of the subjects complete the study.

The trial consists of a screening phase, treatment phase, and safety follow-up phase. Pharmacotherapy is administered according to the trial protocol, followed by corresponding follow-up and examinations as specified in the trial schedule. During the study period, if the investigator determines that the subject indeed requires rescue antiemetic medication, rescue treatment may be provided based on clinical circumstances. The specific type, administration method, dosage, and frequency of the medication are determined by the investigator.

Study period: June 2025-September 2026

3.1 Selection Criteria

Participants must meet all the following inclusion criteria simultaneously during screening and randomization to be eligible for enrollment in this study:

(1) Age ≥18 years, with no gender restriction;

(2) Locally advanced/metastatic esophageal cancer and lung cancer confirmed by histology or cytology, and treated as first-line therapy;

(3) Planned to receive at least 4 cycles of chemotherapy based on cisplatin and carboplatin combined with immunotherapy;

(4) Expected survival duration ≥3 months;

(5) Eastern Cooperative Oncology Group (ECOG) physical status score of 0 or 1;

(6) Good organ function, meeting the following criteria:

a: Neutrophil count $\geq 1.5 \times 10^9$/L;

b: Hemoglobin ≥ 90 g/L;

c: Platelet count ≥ 100×10^9/L;

d: Total bilirubin ≤1.5×ULN;

e: In patients without known liver metastases, aspartate aminotransferase (AST) ≤ 2.5 × ULN and/or alanine aminotransferase (ALT) ≤2.5 ×ULN (for patients with liver metastases, the limit may be relaxed to ≤5×ULN);

f: Serum creatinine ≤1.5×ULN or creatinine clearance rate ≥50 ml/min;

g: Electrocardiogram (ECG): QTc ≤450 ms (male), QTc ≤470 ms (female);

h: Echocardiography: LVEF (left ventricular ejection fraction) ≥50%;

(7) Female participants of reproductive age, as well as male participants whose partners are women of reproductive age, must have employed an effective contraceptive measure from the time of signing the informed consent form until 6 months after the last dose administration. Female participants of reproductive age must have a negative blood pregnancy test result within 72 hours prior to randomization and must not be in the lactation period.

(8) Clearly understand and voluntarily participate in this study, and sign the informed consent form personally.

3.2 Exclusion Criteria

Participants who meet any of the following criteria during screening and randomization are ineligible to participate in this study:

(1) Received or planned to receive abdominal (including diaphragmatic plane and below) or pelvic radiotherapy within the previous 7 days prior to randomization, or during days 1 to 8 of treatment;

(2) Schedule administration of highly emetogenic chemotherapy agents within days 2 to 8 after platinum infusion;

(3) Planned to receive chemotherapy regimens including conventional paclitaxel (using castor oil as solvent);

(4) Randomly administer drugs with potential antiemetic effects within the preceding 2 days: first-generation 5-HT3 receptor antagonists (e.g., ondansetron), phenothiazines (e.g., prochlorazine), butyrophenones (e.g., haloperidol), benzamide derivatives (e.g., metoclopramide), domperidone, cannabinols, traditional Chinese medicines with potential antiemetic effects, scopolamine, and cecirizine.

(5) Had started treatment with benzodiazepines or opioid preparations within the preceding 2 days (excluding triazolam, temazepam, or midazolam taken alone daily);

(6) Subjects who began morphine use within the preceding 7 days (excluding those on stable dosage regimens);

(7) Received systemic corticosteroid therapy (including but not limited to dexamethasone, hydrocortisone, methylprednisolone, or prednisolone) or sedative antihistamines (such as diphenhydramine) within the preceding 7 days (Note: Single-dose steroid administration for contrast agent allergy prophylaxis and topical or inhaled administration are permitted), except for cases requiring hormone pretreatment on the day before chemotherapy.

(8) Palonosetron use within the preceding 14 days;

(9) Use of NK-1 receptor antagonists within the preceding 28 days;

(10) Use of specific CYP3A4 substrates (terfenadine, cisapride, astemizole) or CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, ketoconazole or itraconazole, diltiazem) within 7 days prior to randomization, or use of CYP3A4 strong inducers (e.g., phenobarbital, rifampin, phenytoin, carbamazepine) or specific CYP2D6 substrates (thiuridazine, pimozide) within 28 days prior to randomization;

(11) Vomiting and/or retching, nausea occurring within the preceding 24 hours;

(12) Subjects with symptomatic brain metastases;

(13) Accompanied by poorly controlled serous cavity effusions, including pleural effusion, ascites, and pericardial effusion (patients with controlled effusions stabilized for ≥2 weeks after treatment may be included);

(14) History of severe cardiovascular disease within the preceding 3 months, including but not limited to acute myocardial infarction (AMI), unstable angina pectoris, significant valvular or pericardial disease, ventricular tachycardia, symptomatic chronic heart failure (New York Heart Association [NYHA] class II to IV), and history of severe cardiac conduction abnormalities (e.g., torsades de pointes).

(15) Randomized prior coexisting poorly controlled hypertension (two consecutive resting systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg);

(16) Patients with concurrent active hepatitis B virus infection (HBV DNA ≥2000 IU/mL or 104 copies/mL), active hepatitis C virus infection (HCV-Ab positive with HCV-RNA ≥ upper limit of normal), acquired immunodeficiency syndrome (AIDS) or positive HIV test results, or positive syphilis test results;

(17) Concomitant diseases contraindicated for dexamethasone administration, such as active infections (e.g., pneumonia) or any uncontrolled conditions (e.g., diabetic ketoacidosis, gastrointestinal obstruction, etc.);

(18) Known contraindications for NK-1 receptor antagonists, 5-HT3 receptor antagonists, or dexamethasone;

(19) Participation in other clinical trials within the preceding 30 days (based on the use of investigational drugs);

(20) Subjects deemed by investigators to have other conditions unsuitable for participation in this study.

3.3 Exit Criteria

Participants may voluntarily withdraw from the trial at any time, or be required to withdraw by investigators due to safety concerns, behavioral reasons, or inability to comply with protocol-specified study visit schedules or procedures at their respective research centers.

Reasons for leaving the study may include:

- The subject voluntarily withdrew and declined further follow-up;
- lost to follow-up;
- die ;
- The sponsor terminated the study prematurely.

If a participant fails to return to the center for follow-up as scheduled, every effort should be made to contact the participant. The investigator should inquire about the reason for withdrawal

and request the participant to return to the center for a withdrawal visit, during which any unresolved adverse events (AEs) should be followed up, if applicable. If the participant refuses to attend further visits at the research center, continued tracking and collection of relevant information should be maintained unless the participant voluntarily withdraws. In such cases, no further study evaluations should be conducted, and no additional data should be collected.

3.4 Medication regimen

Queue 1:

- Phosphorotapiratam Palonosetron for Injection: Administered via intravenous infusion for 1 hour (+10 minutes), once before each chemotherapy cycle.
- Dexamethasone acetate: Oral administration of 12 mg on the first day of each chemotherapy cycle prior to chemotherapy, followed by 3.75 mg twice daily (bid) on days 2-4.

Queue 2:

- Fosapiritan and Nifedipine for Injection: 150 mg, administered via intravenous infusion over 20-30 minutes, once before each chemotherapy cycle.
- Palonosetron hydrochloride: 0.25 mg, administered via intravenous push infusion for at least 30 seconds, once before each cycle of chemotherapy.
- Dexamethasone acetate: Oral administration of 6 mg on the first day of each chemotherapy cycle prior to chemotherapy, 3.75 mg once on the second day, and 3.75 mg twice daily (bid) on days 3-4.

3.5 Study Endpoints

Primary efficacy endpoint

The proportion of subjects achieving complete remission (CR: no vomiting and no rescue therapy) with an ultra-long delay period (120 h- 168 h) after chemotherapy initiation in each immunotherapy plus chemotherapy cycle.

Secondary efficacy endpoint

(1) CR rates during the acute phase (0-24 h), delayed phase (24 h- 120 h), overall phase (0- 120 h), and 0- 168 h periods of each immunotherapy + chemotherapy cycle;

(2) Comparison of the time to first vomiting using Kaplan-Meier curves;

(3) Assess the impact of chemotherapy-induced nausea and vomiting on quality of life using the Functional Life Index-Vomiting (FLIE);

(4) Incidence of adverse events and serious adverse reactions throughout the study period, such as safety concerns including prolonged Q-T interval and constipation.

3.6 Statistical Analysis

Count data were summarized using frequency and percentage. Measurement data were summarized using mean, standard deviation, median, maximum value, and minimum value. Statistical analysis was performed using SAS 9.4 software.

Population analysis

Full Analysis Set (FAS): Includes all enrolled subjects who received the investigational drug,

with primary efficacy analysis based on FAS.

Safety Analysis Set (SS): Includes all enrolled subjects who received at least one dose of the study drug.

Efficacy Analysis

If a participant's assessment of vomiting episodes is missing on any day during the overall period, resulting in an inability to determine whether the participant has achieved complete remission, the participant is recorded as having incomplete remission.

Sensitivity analysis for primary estimation targets: The sensitivity analysis methodology is identical to that of the primary estimation method, with only differences in the missing value imputation rules. If a participant's assessment of vomiting episodes is missing on any day during the study period, complete remission is determined based on the available data from that participant.

If the subject's assessment of vomiting episodes is missing on any day within the extended delay period, resulting in an inability to determine whether the subject has achieved complete remission, the subject is recorded as having incomplete remission.

safety analysis

AEs will be coded using the MedDRA dictionary. The frequency and incidence of treatment-emergent adverse events (TEAEs) will be summarized by grouping according to System Organ Classification (SOC), preferred terms, and severity. Outcomes such as vital signs, electrocardiogram (ECG), and other clinical laboratory tests will be summarized by relative changes from baseline. Additionally, abnormal clinical laboratory test results will be described in a separate table.

4 Sample Size Calculation

This study adopted a randomized, parallel, cohort design. Based on data from previous Phase III studies, the super-delayed complete response (CR) rate for HR20013+ dexamethasone in the first cycle for preventing nausea and vomiting induced by highly emetogenic chemotherapy was 90.3%, while the CR rate for fosapitant + dexamethasone + palonosetron was 86.5%. With a planned enrollment of 57 subjects per group, the 95% confidence interval (CI) width for the CR rates in both groups could be maintained within 0.2. Considering a 5% dropout rate, a total of 60 subjects were enrolled per group, resulting in a total of 120 subjects.

5 Data Management and Confidentiality

The sponsor was responsible for the clinical trial data management in this study, utilizing an Electronic Data Collection (EDC) system for data collection and management. All records pertaining to subject identity were kept confidential and not disclosed beyond the scope permitted by applicable laws and/or regulations.

5.1 Data Collection

The electronic Case Report Form (eCRF) shall be completed by investigators or data entry personnel through the Electronic Data Capture (EDC) system. eCRFs must be filled out promptly, with ensured traceability of data from original documents or records. When modifying data in the EDC system, the reasons for modifications must be documented according to system prompts. Modification history and rationale shall be recorded in the EDC system's audit trail. Investigators or their authorized personnel are required to verify the authenticity, completeness, and timeliness of eCRF data and affix electronic signatures within the EDC system.

Data administrators established electronic case report forms (eCRFs) and logical verification procedures in the Electronic Data Capture (EDC) system in accordance with the study protocol, completing user acceptance testing and system deployment prior to the first participant enrollment. All EDC users must complete relevant training and archive training records to obtain access permissions for the study's eCRFs. When implementing electronic signatures on eCRFs, users must confirm and agree to the electronic signature usage statement. Accounts are restricted to individual users only, with passwords requiring secure storage and regular renewal. Permissions must be promptly revoked when there are personnel changes within the research team.

5.2 Data Management

The logical verification program of the EDC system conducts integrity and logical checks on entered data, raising questions about potentially problematic entries. Researchers or data entry personnel may correct data or provide explanations and confirmations by responding to these queries. Researchers must promptly address questions from both the system and data reviewers, and may raise follow-up questions multiple times as needed until all data issues are resolved.

Forty percent of participants will undergo an interim analysis upon completing the study. Prior to database locking, the research team must complete data cleaning, compile all protocol deviation events occurring during the trial, and convene a data review meeting to determine the analytical population. All decisions made during the data review meeting must be documented in written records. Following approval of the data review meeting, the research team will confirm the locking of the study database in the Electronic Data Capture (EDC) system. Once locked, the data cannot be modified.

Upon completion of the study, the storage and management of research materials must comply with Good Clinical Practice (GCP) requirements. Investigators must notify the sponsor in advance when destroying any study-related documents or records. After the investigational drug is approved for marketing, or even if the clinical study is terminated prematurely, the sponsor shall retain clinical trial data for at least 5 years.

6 Previous and concomitant therapies

6.1 Previous Treatment

Information on medication and non-pharmacological treatments administered by subjects during the 30 days prior to randomization must be recorded in the Electronic Case Report Form

(eCRF). Prohibited treatments and prohibited medications prior to randomization were consistent with the exclusion criteria.

6.2 Remedial Treatment

Remedial treatment is defined as any prescription medication prescribed by the investigator to alleviate nausea/vomiting. This definition must be explained to the subject. During the study period, investigators evaluate the reported severity of nausea/vomiting and observed clinical manifestations. Remedial treatment for nausea/vomiting may be administered only when necessary based on investigator judgment, and must not be used if the subject does not exhibit such symptoms. When administering remedial treatment, 5-HT3 receptor antagonists (excluding palonosetron) are recommended as the first-line option.

6.3 Contraindicated Medications in the Study

1. The use of rescue medications for non-rescue purposes is prohibited during chemotherapy;
2. During chemotherapy cycles, the use of medications containing rolapitan, palonosetron, or dexamethasone is prohibited except for visits specified in the treatment regimen.
3. The following medications are prohibited during the study period:

(1) Specific CYP3A4 substrates: terfenadine, cisapride, astemizole;

(2) Strong CYP3A4 inducers: phenobarbital, rifampin, phenytoin, and carbamazepine;

(3) CYP3A4 inhibitors: ritonavir, clarithromycin, ketoconazole, itraconazole, diltiazem, etc.;

(4) Specific CYP2D6 substrates: thioridazine, pimozide.

7 Informed Consent

The rights, safety, and physical/mental well-being of participants are paramount considerations, taking precedence over scientific and societal benefits. After explaining the fundamental aspects of the study and confirming participants' understanding of its objectives, investigators must require each participant to sign their name and date on the Informed Consent Form (ICF). Participants should carefully review and consider their informed consent statement before signing, and obtain a signed ICF. Prior to initiating any clinical study-related procedures, a signed ICF must be obtained from participants, including informed consent for any screening processes conducted to determine eligibility for study participation. Participants may not proceed with the study without obtaining informed consent.

For subjects who are unable to sign the informed consent form independently for any reason, the legal guardian must sign on their behalf. The ICF signed by the subject and the investigator with their names and dates must be properly retained by the investigator and documented in the relevant original research records.

The confidentiality of subject information is strictly enforced by investigators, participating researchers, and their agents. Confidentiality also extends to biological samples and genetic testing beyond clinical subject data. Consequently, the study protocol, documentation, data, and all other generated information will be rigorously protected. No relevant study or data information may be

disclosed to unauthorized third parties without written approval. The research data entry and management systems utilized by clinical research centers and researchers at the Second Affiliated Hospital of Zhejiang University School of Medicine are password-protected and configured with confidentiality settings. Upon study completion, all identifying information in research databases will be anonymized and archived at the Second Affiliated Hospital of Zhejiang University School of Medicine.

8 Adverse Event Reporting

8.1 Adverse Events

Adverse events (AEs) refer to all adverse medical events occurring in subjects after receiving the investigational drug, which may manifest as symptoms, signs, diseases, or abnormal laboratory findings, but not necessarily have a causal relationship with the investigational drug. AEs include, but are not limited to:

(1) Worsening of pre-existing medical conditions/diseases (including exacerbation of symptoms, signs, and abnormal laboratory findings) prior to enrollment in clinical trials;

(2) Any newly occurring adverse event (AE): Any newly occurring adverse medical condition (including symptoms, signs, and newly diagnosed diseases);

(3) Abnormal laboratory test values or results with clinical significance (known prior to screening or newly identified during screening as comorbidities or baseline conditions, not recorded as adverse events [AEs]).

8.2 Severity and Criteria for Adverse Events

Refer to the NCI-CTCAE 5.0 version classification criteria for drug adverse events (AEs). For AEs not listed in the NCI-CTCAE 5.0 table, the following criteria may be applied:

grade	Clinical description of severity
1	Mild: No clinical symptoms or only mild clinical symptoms; only clinical or laboratory abnormalities; no treatment required
2	Moderate: Requires minor, localized, or non-invasive treatment; age-appropriate instrumental activities of daily living (ADLs) are limited, including instrumental daily activities such as cooking, shopping, making phone calls, and counting money.
3	Severe illness or medically significant symptoms that are not immediately life-threatening; leading to hospitalization or prolonged hospital stay; resulting in disability; impairing daily activities of living (Selfcare ADL). Daily activities of living refer to: bathing, dressing, undressing, eating, using the toilet, taking medication, etc., without requiring bed rest.
4	Life-threatening; requires emergency treatment
5	Adverse Events Leading to Death

Abbreviations: AE = adverse event; ADL = activities of daily living.

8.3 Assessment of Causality Between Adverse Events and Investigational Drug

The determination of causality between adverse events (AEs) and investigational drugs

involves comprehensive evaluation to assess whether there is a reasonable likelihood that the investigational drug caused or contributed to the AEs. Key factors include whether the AEs occurred in a reasonable temporal sequence relative to drug administration, the characteristics of the investigational drug, its toxicological and pharmacological effects, concomitant medication use, the subject's underlying diseases, medical history, family history, and desensitization/reexposure reactions. Typically, evidence or arguments supporting causality determination should be provided.

The causal relationship between AE and the investigational drug should be assessed by the investigator as "definitely associated", "possibly associated", "possibly unrelated", "definitely unrelated", or "uncertain".

8.4 Serious Adverse Events

A Serious Adverse Event (SAE) is any of the following adverse medical events occurring in a subject after receiving any dose of the investigational drug:

(1) Leading to death;

(2) Life-threatening (defined as the subject being at risk of death at the time of event occurrence, without implying that worsening of the condition would necessarily lead to death);

(3) Requires hospitalization or prolonged hospital stay;

(4) Permanent or apparent disability/function loss;

(5) Congenital anomalies/birth defects;

(6) Other significant medical events.

8.5 Reporting System

Various adverse events: Take timely measures to manage them and record them in the case report form.

Serious Adverse Event (SAE): Immediate measures should be taken for management, with records documented in the case report form. The investigator shall determine whether to discontinue or reduce medication, and promptly report to the ethics committee, clinical trial site, and sponsor. A report must be submitted to the national and provincial food and drug regulatory authorities within 24 hours. SAEs must be reported via the "In-Hospital Network Adverse Event and Near-Miss Error Non-Blame Reporting System." Specific procedures are illustrated in the following diagram.

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Appendix I: ECOG Physical Status Score

Prior to treatment, an assessment of the patient's general health status should be conducted. A key indicator of general health status is the evaluation of performance status (PS), which reflects the patient's physical condition and serves as an indicator of their tolerance to treatment. The Eastern Cooperative Oncology Group (ECOG) has developed a simplified performance status scoring system, as shown in the table below:

ECOG Physical Status Score Criteria

Activity Score	description
0	Asymptomatic, with full voluntary movement and the ability to perform unrestricted activities.
1	Symptomatic, fully capable of walking, but with limited capacity for heavy physical activities. Able to perform light or sedentary tasks, such as minor household chores or office work.
2	Symptomatic, able to walk and perform daily activities independently, but unable to engage in any physical activity. Approximately 50% of the time is spent conscious (daytime bed rest <50%).
3	Symptomatic, with limited ability for self-care, bedridden or sitting for>50% of waking hours, but not yet bedridden.
4	Complete loss of function, inability to perform any self-care activities, and bedridden status.
5	die 。

Appendix II: Functional Life Impact of Vomiting Scale (FLIE)

The Vomiting Life Impact Scale (FLIE) is a patient-reported questionnaire designed to assess the quality of life affected by nausea and vomiting. The questionnaire consists of 18 questions, divided into two sections: nausea and vomiting, with 9 questions in each section. See the table below for details.

Each question was evaluated using an intuitive simulation scale. Carefully read the questions, as in some items, a "1" indicates no impact on your quality of life, while in others, a "1" signifies a significant impact. The numerical value increases progressively with higher scores, with "7" representing the opposite meaning of the aforementioned "1". Nausea scores, vomiting scores, and total scores were calculated by summing responses across categories and the total number of responses. Scoring was performed before each chemotherapy cycle, 24 hours after chemotherapy, 120 hours after chemotherapy, and 168 hours after chemotherapy.

Participants must draw vertical lines on the intuitive simulation scale when responding. The operational example is as follows:

Vomiting Life Functioning Inventory (FLIE)

1: Have you experienced nausea during the following periods: before chemotherapy/within 1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 days after chemotherapy initiation (120-168 hours)?

1 2 3 4 5 6 7

Not very large at all Not very large at all

2: Did your nausea affect your ability to continue normal recreational or leisure activities during the following periods: before chemotherapy/1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 days after chemotherapy initiation (120-168 hours)?

1 2 3 4 5 6 7

Not very large at all Not very large at all

3: During the period before chemotherapy/1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 days after chemotherapy initiation (120-168 hours), did your nausea affect your ability to prepare a meal or perform light household tasks?

1 2 3 4 5 6 7

Very large, not at all Very large, not at all

4: How much did your nausea afect your ability to eat during the following periods: before chemotherapy/1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 days after chemotherapy initiation(120-168hours)?

1 2 3 4 5 6 7

Not very large at all Not very large at all

5: To what extent does your nausea afect your ability to consume beverages during the following periods: before chemotherapy/1 day after chemotherapy initiation(0-24 hours)/2-5 days after chemotherapy initiation(24-120 hours)/6-7 daysafterchemotherapyinitiation(120-168hours)?

1 2 3 4 5 6 7

Not very large at all Not very large at all

6: How much does your nausea affect your willingness to visit and spend time with family and friends before chemotherapy, within 1 day after chemotherapy initiation (0-24 hours), within 2-5 days after chemotherapy initiation (24-120 hours), or within 6-7 days after chemotherapy initiation (120-168 hours)?

1 2 3 4 5 6 7

Very large, not at all Very large, not at all

7: Did your nausea affect your daily activities during the following periods: before chemotherapy/1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 days after chemotherapy initiation (120-168 hours)?

1 2 3 4 5 6 7

Not very large at all Not very large at all

8: Please evaluate the degree of distress caused by your nausea to you personally during the following periods: within 1 day before chemotherapy/after chemotherapy initiation (0-24 hours), 2-5 days after chemotherapy initiation (24-120 hours), and 6-7 days after chemotherapy initiation (120-168 hours).

1 2 3 4 5 6 7

Not very large at all Not very large at all

9: Please assess the degree of difficulty your nausea has caused to the lives of your closest loved ones during the following periods: within 1 day before chemotherapy/after chemotherapy initiation (0-24 hours), 2-5 days after chemotherapy initiation (24-120 hours), and 6-7 days after chemotherapy initiation (120-168 hours).

1 2 3 4 5 6 7

Not very large at all Not very large at all

10: Have you experienced vomiting during the following periods: before chemotherapy/within 1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 days after chemotherapy initiation (120-168 hours)?

1 2 3 4 5 6 7

Not very large at all Not very large at all

11: Did vomiting afect your ability to continue normal recreational or leisure activities during the following periods: before chemotherapy/within 1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 days after chemotherapy initiation (120-168 hours)?

1 2 3 4 5 6 7

Very large, not at all Very large, not at all

12: Did your vomiting condition affect your ability to prepare a meal or perform light household tasks during the following periods: before chemotherapy/1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 days after chemotherapy initiation (120-168 hours)?

1 2 3 4 5 6 7

Not very large at all Not very large at all

13: How much did your vomiting afect your ability to eat during the folowing periods: before chemotherapy/1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 days after chemotherapy initiation(120-168hours)?

1 2 3 4 5 6 7

Not very large at all Not very large at all

14: How much did your vomiting afect your ability to consume beverages during the folowing periods: before chemotherapy/1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 daysafterchemotherapyinitiation(120-168hours)?

1 2 3 4 5 6 7

Not very large at all Not very large at all

15: How much does your vomiting condition affect your willingness to visit and spend time with family and friends before chemotherapy, within 1 day after chemotherapy initiation (0-24 hours), within 2-5 days after chemotherapy initiation (24-120 hours), or within 6-7 days after chemotherapy initiation (120-168 hours)?

1 2 3 4 5 6 7

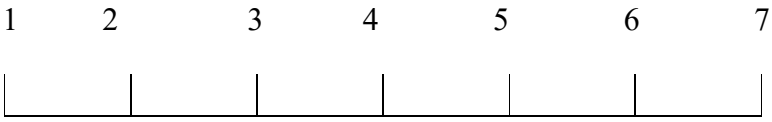
Very large, not at all Very large, not at all

16: Did vomiting affect your daily activities during the following periods: before chemotherapy/within 1 day after chemotherapy initiation (0-24 hours)/2-5 days after chemotherapy initiation (24-120 hours)/6-7 days after chemotherapy initiation (120-168 hours)?

1 2 3 4 5 6 7

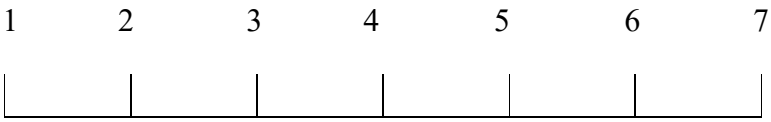
Not very large at all Not very large at all

17: Please assess the degree of personal distress caused by vomiting during the following periods: within 1 day before chemotherapy/after chemotherapy initiation (0-24 hours), 2-5 days after chemotherapy initiation (24-120 hours), and 6-7 days after chemotherapy initiation (120-168 hours).



Not very large at all Not very large at all

18: Please assess the degree of difficulty your vomiting has caused to the lives of your closest loved ones during the following periods: within 1 day before chemotherapy/after chemotherapy initiation (0-24 hours), 2-5 days after chemotherapy initiation (24-120 hours), and 6-7 days after chemotherapy initiation (120-168 hours).



Very large, not at all Very large, not at all