

Original Article

Efficacy and safety of a two- versus single-dose submicron aprepitant injection regimen in preventing chemotherapy-induced nausea and vomiting in patients undergoing highly emetogenic chemotherapy: a randomized controlled trial

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Abstract: Objectives: This study evaluates the comparative efficacy and safety profiles of a two-dose (TD) versus single-dose (SD) submicron aprepitant injection regimen for preventing chemotherapy-induced nausea and vomiting (CINV) in patients subjected to highly emetogenic chemotherapy (HEC). Methods: A total of 199 patients were enrolled in this open-labeled trial (ChiCTR2500104533) and randomly assigned to either the TD (130 mg on Days 1 and 3) or SD group (130 mg on Day 1) in combination with palonosetron and dexamethasone. The duration of complete response (CR), defined as the time to the first episode of vomiting or rescue medication use, was designated as the primary endpoint. Secondary endpoints comprised the CR rates, complete control, and nausea control, each of which was evaluated separately during the acute, delayed, and overall phases. Results: The CR duration was significantly longer in the TD group than in the SD group (13.39 ± 4.26 vs. 10.89 ± 6.27 days; $P < 0.01$). The TD regimen also was associated with higher CR rates in the delayed phase (93.0% vs. 74.7%; $P < 0.001$) and across the entire observation period (87.0% vs. 68.7%; $P < 0.01$). The TD schedule also achieved a superior CR rate at Day 5 (89.2% vs. 55.9%; $P < 0.01$) in the prespecified subgroup of patients receiving multiday chemotherapy. Safety profiles were comparable between the two groups. Conclusions: The TD aprepitant regimen provides significantly superior and sustained CINV control across all phases, with a favorable safety profile. This strategy thus represents a more effective and reliable option for HEC patients, especially for those on multiday regimens.

Keywords: Chemotherapy-induced nausea and vomiting, aprepitant, antiemetic, randomized controlled trial, highly emetogenic chemotherapy, submicron emulsion, neurokinin-1 receptor antagonist

Introduction

In patients receiving highly emetogenic chemotherapy (HEC), including cisplatin-based regimens and anthracycline-cyclophosphamide (AC) combinations, chemotherapy-induced nausea and vomiting (CINV) remains one of the most frequent and debilitating adverse effects of systemic anticancer treatment. Moderately emetogenic chemotherapy (MEC), including carboplatin, oxaliplatin, and irinotecan, can also cause substantial nausea and vomiting when prophylaxis is inadequate [1]. Regardless of emetogenic risk level, CINV substantially compromises quality of life and reduces treat-

ment adherence, and may necessitate chemotherapy dose reductions or treatment discontinuation.

CINV is generally classified into acute (< 24 hours post-chemotherapy) and delayed (> 24 hours, typically peaking at 48-72 hours and persisting for 6-7 days) [2]. Although considerable advances in antiemetic management in acute CINV [3, 4] delayed CINV occurring in the outpatient setting is often suboptimally controlled due to the lack of direct clinical supervision [5]. This can lead to dehydration, electrolyte disturbances, and malnutrition, potentially necessitating chemotherapy dose reductions

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Table 1. Baseline demographic and clinical characteristics

	TD (N = 100)	SD (N = 99)	Overall (N = 199)	Statistic (χ^2/t)	P
Age [mean (SD)], years	59.92 (10.30)	60.28 (10.03)	60.10 (10.14)	T = 0.27	0.7873
Age < 18 years, n (%)	0 (0)	0 (0)	0 (0)		
Age 18-40 years, n (%)	5 (5.0)	6 (6.1)	11 (5.5)		
Age 41-64 years, n (%)	55 (55.0)	53 (53.5)	108 (54.3)		
Age 65-75 years, n (%)	38 (38.0)	39 (39.4)	77 (38.7)		
Age > 75 years, n (%)	2 (2.0)	1 (1.0)	3 (1.5)		
Sex, n (%)				$\chi^2 = 0.05$	0.8191
Male	42 (42.0)	40 (40.4)	82 (41.2)		
Female	58 (58.0)	59 (59.6)	117 (58.8)		
Ethnicity, n (%)					> 0.9999
Han	99 (99.0)	99 (100)	198 (99.5)		
Other	1 (1.0)	0 (0)	1 (0.5)		
Multiday chemotherapy regimen, n (%)	51 (51.0)	45 (45.5)	96 (48.2)	$\chi^2 = 0.61$	0.4338
Chemotherapy regimen ≥ 3 days, n (%)	37 (37.0)	34 (34.3)	71 (35.7)	$\chi^2 = 0.15$	0.6957

Note: Continuous variables were analyzed using the independent samples t-test, and categorical variables were analyzed using the Pearson Chi-square test. Statistical values are reported in the P-value column.

or discontinuation. In addition, untimely and inadequate CINV management increases the subsequent healthcare costs and imposes a substantial burden on the healthcare system. The growing shift towards outpatient chemotherapy has further compounded these challenges, underscoring the urgent need for extended antiemetic prophylaxis [6].

The selective neurokinin-1 receptor antagonist (NK-1RA), aprepitant, is recommended for HEC and selected MEC regimens by most international guidelines [7]. However, the conventional single-dose regimen is often insufficient for delayed and long-delayed CINV or patients receiving multiday chemotherapy [8]. Therefore, a modified regimen, such as repeated or extended dosing, may offer enhanced protection without compromising the safety profile [9].

To answer this question, here we designed a prospective, randomized, open-label, parallel-controlled study to investigate the benefits of a two-dose aprepitant regimen in HEC patients. We specifically extended follow-up and included multiple chemotherapy cycles to evaluate the long-term and cumulative effects. By tackling the major limitations in delayed-phase control and adopting a practical dosing strategy, our study provides robust evidence that may inform future updates to antiemetic guidelines.

Should our findings be validated, the two-dose regimen could be readily incorporated into existing antiemetic protocols.

Methods

Study design

The single-center, prospective, randomized, open-label, parallel-controlled trial (ChiCTR25-00104533) was conducted at the Affiliated Hospital of Jiangsu University from October 2024 to June 2025. This study was approved by the Institutional Ethics Committee of the Affiliated Hospital of Jiangsu University (Approval No. KY2024H0923-07). All procedures were in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment. This regional tertiary cancer center serves eastern Jiangsu Province, with a catchment population of roughly 30 million; approximately 70% of patients are local residents, and the remaining 30% are referred from surrounding cities. **Table 1** shows that our cohort's baseline demographic and clinical characteristics were comparable to the national registry data for Chinese HEC patients, supporting generalizability to similar clinical settings.

Of note, here we adopted a novel submicron emulsion (SME) for aprepitant injection to elimi-

nate polysorbate 80 and other excipients commonly linked to injection site reactions. This strategy allows rapid intravenous push administration (within 2 minutes) without compromising pharmacokinetics, a strategy that greatly improves clinical convenience and patient comfort. The SME technology exemplifies the integration of nanobiotechnology and pharmaceutical engineering into the development of improved supportive care therapeutics.

We planned to enroll and randomize a total of 200 patients in a 1:1 ratio. Patients who signed informed consent underwent eligibility screening based on predefined inclusion and exclusion criteria. We reconfirmed eligibility on Day 1 of the first chemotherapy cycle, after which we randomized eligible participants to either the two-dose (TD) group or the single-dose (SD) group.

Patients

Sample size estimation was based on the primary endpoint: the duration of complete response (CR) in days. Assuming a mean difference of 3 days between the two groups based on preliminary observational data, with a standard deviation of approximately 5 days, a two-sided significance level (α) of 0.05, and a power ($1-\beta$) of 80%, a minimum of 88 participants (44 per group) would be required to detect a statistically significant difference using a two-sample t-test. Therefore, we expected 200 participant enrollment (100 per group) to allow for possible dropouts and protocol deviations.

Eligible patients were adults aged 18-75 years with histologically or cytologically confirmed malignancy requiring HEC. Key inclusion criteria were: (1) adults (18-75 years old) receiving HEC; (2) life expectancy longer than 3 months, and (3) able to comply with the study procedures. All participants agreed to use effective contraception throughout the study period.

Key exclusion criteria included chronic gastrointestinal disorders or vestibular diseases likely causing recurrent nausea and vomiting, participation in other interventional clinical trials; uncontrolled cancer-related pain requiring opioid dose titration; nausea or vomiting within 72 hours prior to enrollment; and inability to complete study questionnaires independently. Participants were excluded if they had received CYP3A4 inhibitors or inducers, or agents

with antiemetic properties within a washout period prior to chemotherapy, or who had known hypersensitivity to any component of the study drugs. Additionally, individuals deemed unsuitable by the investigator for any reason were excluded.

Randomization

We performed block randomization using the PROC PLAN procedure in SAS software. A total of 200 eligible patients were randomly assigned in a 1:1 ratio to either the TD or the SD group (100 patients per group). Randomization was conducted on Day 1 of the first chemotherapy cycle following confirmation of eligibility and informed consent, via a centralized randomization system.

Antiemetic treatment regimen

For the first chemotherapy cycle, participants were randomized to receive one of the following antiemetic regimens: the TD group received aprepitant injection (Enqihui®, 18 mL:130 mg, Nanjing Entai Medical Science & Technology Co., Ltd.) 130 mg intravenously on Day 1 and 3 (QD), while the SD group received aprepitant injection 130 mg intravenously on Day 1 only.

To ensure consistency and efficiency in clinical practice, we administered all injections as 2-minute intravenous (IV) pushes via peripheral or central venous access. Bioequivalence between the 2-minute IV push and the standard 30-minute infusion has been established in healthy subjects, confirming that the shorter administration route does not compromise pharmacokinetic performance [10].

Both groups received concomitant palonosetron hydrochloride and dexamethasone. Palonosetron hydrochloride 0.25 mg was administered intravenously on Day 1 (QD) in both groups, approximately 30 minutes prior to chemotherapy. Dexamethasone was administered orally at 6 mg on Day 1 and 3.75 mg once daily (QD) on Days 2 to 4 in the TD group. In the SD group, patients received 6 mg on Day 1, 3.75 mg QD on Day 2, and 3.75 mg twice daily (BID) on Day 3 and 4.

End points

The primary endpoint was the duration of CR, defined as the time interval from the initiation

of chemotherapy to the first occurrence of vomiting (including retching) or the use of rescue therapy intended to treat nausea or vomiting.

Secondary endpoints included: (1) CR rates on Day 1, Days 2-5, and Days 6-14; (2) complete control (CC) rates, defined as the absence of vomiting, no more than mild nausea, and no use of rescue therapy; (3) nausea control rates, defined as no more than mild nausea and no use of rescue treatment; (4) the duration of CR; (5) the duration of CC; (6) the duration of nausea control; (7) the number of rescue therapy administrations and (8) the time to first rescue medication use during the acute (Day 1), delayed (Days 2-5), and long-delayed (Days 6-14) phases; (9) the daily frequency and severity of vomiting; (10) the incidence of CINV within 120 hours after the subsequent chemotherapy cycle (in which all patients received a single-dose aprepitant regimen).

We performed a subgroup analysis in patients receiving multiday chemotherapy regimens (lasting more than three days), using the same efficacy endpoints described above.

Safety assessments included monitoring of vital signs and adverse events. We graded adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, and evaluated nausea and vomiting using CTCAE version 4.0.

Statistical analysis

Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). A two-sided significance level of 0.05 was used unless otherwise specified.

Efficacy analyses were based on the full analysis set (FAS), which included all randomized participants who received at least one dose of the study medication. Baseline characteristics were summarized using descriptive statistics. We analyzed the duration of CR using the Kaplan-Meier method and evaluated group differences using the log-rank test.

Secondary outcomes, such as CR, CC, and nausea control rates, were compared using chi-square (χ^2) tests with 95% confidence intervals calculated by binomial distribution. Continuous variables were analyzed using

t-tests or Wilcoxon rank-sum tests, as appropriate. Subgroup analyses were performed for participants receiving multiday chemotherapy regimens. The delayed-phase complete response rate (Day 2-5) was pre-specified as the key secondary endpoint. Benjamini-Hochberg false discovery rate (BH-FDR) adjusted *p*-values ($q = 0.05$) are presented in [Supplementary Table 1](#) for all 15 secondary-endpoint comparisons in the overall analysis (3 endpoints $\times$ 5 time intervals, treated as a single family). All other subgroup and multiple time-point comparisons remain exploratory and were not adjusted for multiplicity; therefore, these results should be interpreted with caution.

Safety analyses were based on the safety set (SS), which comprised all randomized patients who received at least one dose of the study drug with available safety data. AEs were classified and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 28.0.

Results

Patient enrollment and baseline characteristics

A total of 200 patients were enrolled and randomized equally into the TD and SD groups ($n = 100$ per group). One patient in the SD group withdrew consent prior to receiving treatment, resulting in a full analysis set (FAS) of 199 patients (TD: $n = 100$, SD: $n = 99$). Patient disposition is detailed in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram ([Figure 1](#)).

Baseline demographic and clinical characteristics were well balanced between groups ([Table 1](#)). The majority of patients were aged 41-64 years (54.3%), with a slight predominance of females (58.8%). Nearly half (48.2%) of patients received multiday chemotherapy regimens, of whom 35.7% had courses lasting ≥ 3 days.

Efficacy

Overall analysis: For the primary endpoint, the TD group had a significantly longer CR duration than the SD group (13.39 ± 4.26 vs. 10.89 ± 6.27 days; $P < 0.01$) ([Figure 2A](#)). Although the median CR duration could not be estimated

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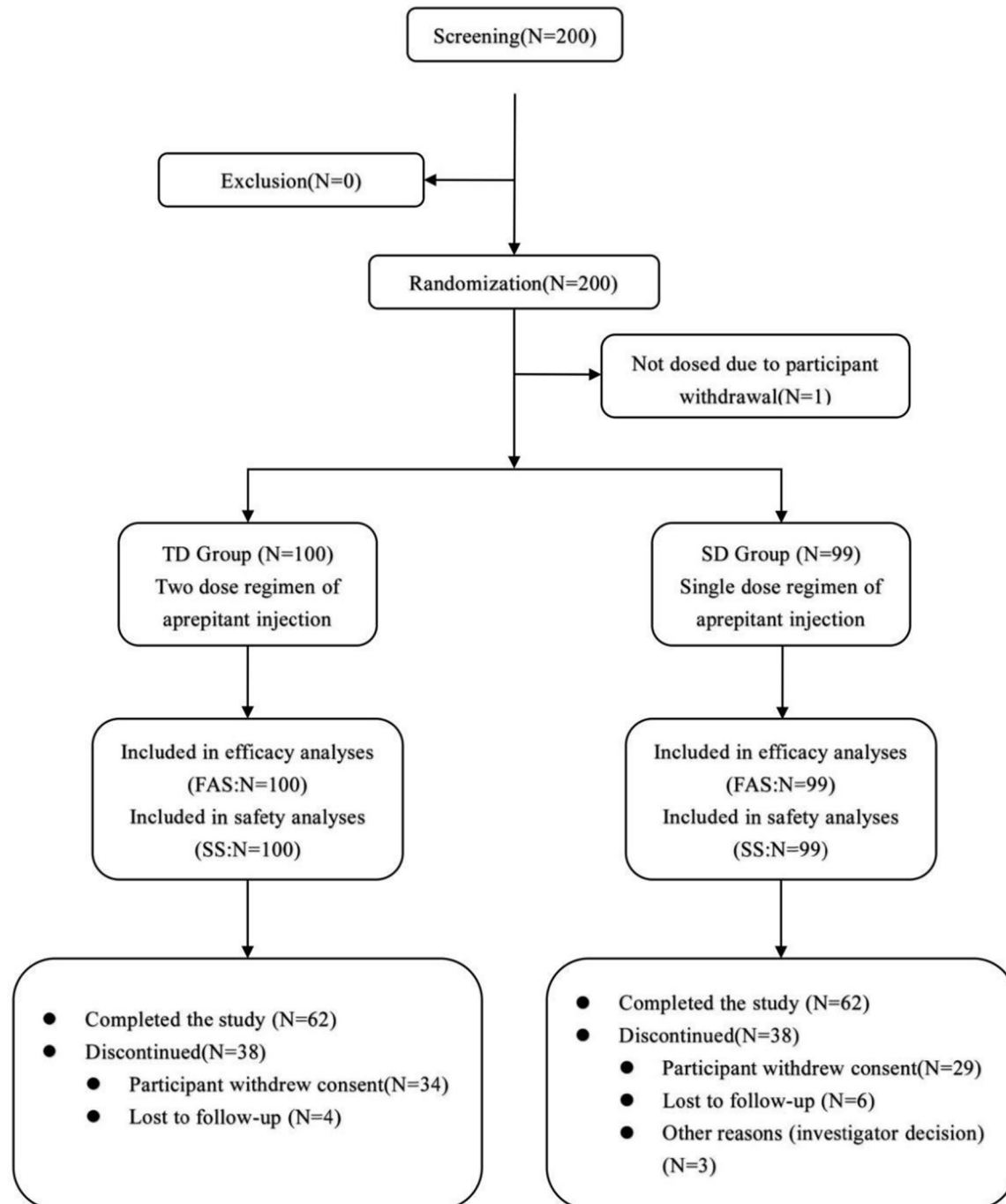


Figure 1. CONSORT flow diagram of patient enrollment, randomization, and follow-up. A total of 200 patients were enrolled and randomly assigned to receive either the two dose (TD, n = 100) or single dose (SD, n = 100) aprepitant. One patient in the SD group withdrew consent before receiving the drug. All 199 patients completed the first chemotherapy cycle and were included in the efficacy and safety evaluation. The discontinuation in the second cycle with specific reasons are detailed in the diagram. TD, two-dose; SD, single-dose; FAS, full analysis set; SS, safety set.

due to the low event rates in both groups by the end of the observation (13.0% in TD and 31.3% in SD group), Kaplan-Meier analysis confirmed

a significant between-group difference ($P = 0.0013$) (Figure 2B; Table 2). These results indicate that the prolongation of the symptom-

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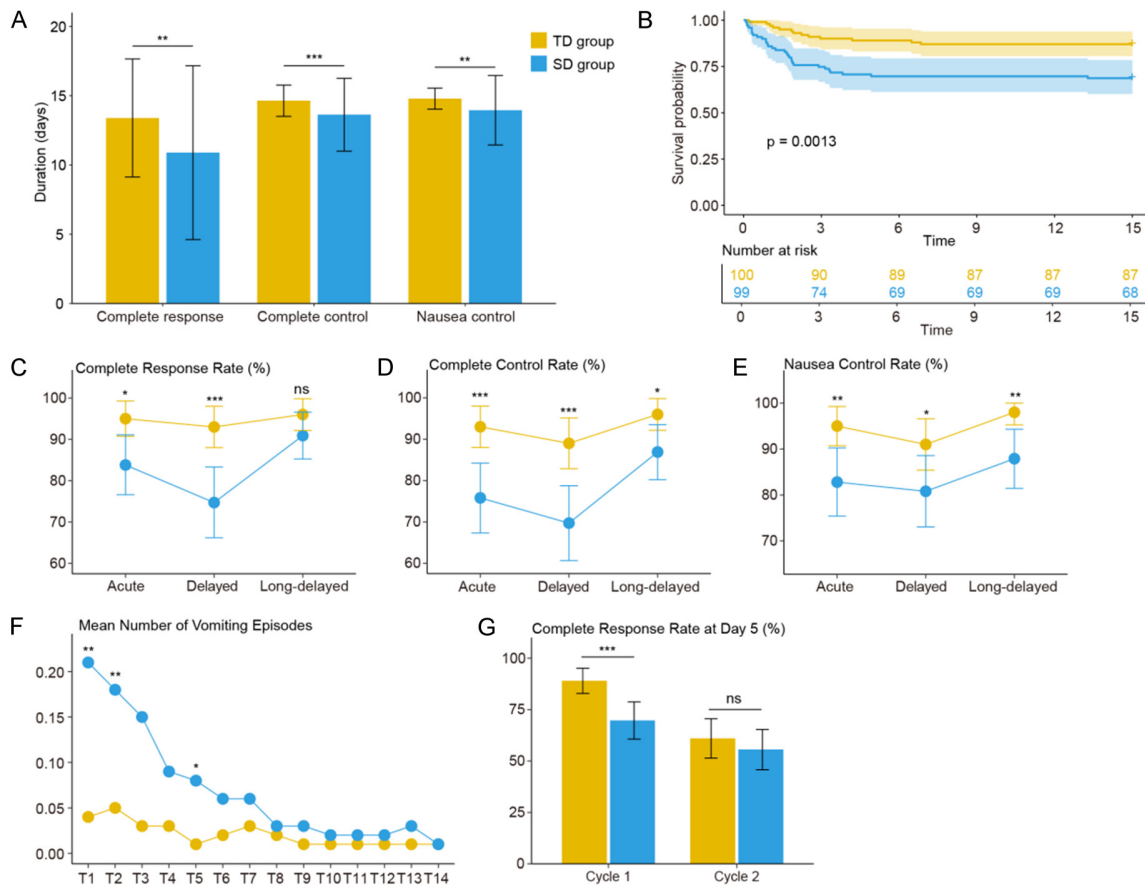


Figure 2. Primary and secondary efficacy endpoints in the overall analysis. (A) Bar plots showing the duration of complete response, complete control and nausea control between treatment groups. (B) Kaplan-Meier analysis of the complete response duration between treatment groups. (C-E) Line graph illustrating complete response (C), complete control (D) and nausea control (E) rates at specified time points following chemotherapy. (F) Line graph depicting the mean daily number of vomiting episodes between treatment groups. (G) Bar plots showing the complete response rates at Day 5 across different chemotherapy cycles between treatment groups. Error bars represent 95% confidence intervals (CIs). Statistical significance is indicated as: ns, no significant difference; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

free time in TD group is clinically meaningful. This 2.5-day difference is particularly valuable during the critical delayed and long-delayed phases.

For secondary efficacy measures, the TD group consistently outperformed the SD group at all evaluated time points, with higher rates of complete response (CR), complete control (CC), and nausea control. Specifically, CR rates were higher in the acute (95.0% vs. 83.8%), delayed (93.0% vs. 74.7%), and long-delayed (96.0% vs. 90.9%) phase in the TD group. This advantage was significant in the acute-plus-delayed (89.0% vs. 69.7%) and the overall period (87.0% vs. 68.7%) as well (Figure 2C; Table 3). Notably, the largest between-group differences were noticed in the delayed and overall phases.

Similarly, both CC and nausea control rates were significantly improved in the TD group during the acute phase, and these benefits persisted throughout the delayed and long-delayed phases (Figure 2D and 2E; Table 3).

Of the 15 secondary-endpoint comparisons in the overall analysis, 14 were significant at the nominal $\alpha = 0.05$ level; all 14 remained significant after BH-FDR adjustment at $q = 0.05$ (Supplementary Table 1). The only comparison that did not reach significance (complete response rate, Day 6-14) was non-significant at both raw ($P = 0.146$) and adjusted ($P_{\text{BH-FDR}} = 0.146$) levels. The pre-specified key secondary endpoint, delayed-phase complete response rate (Day 2-5), remained highly significant after multiplicity adjustment ($P_{\text{BH-FDR}} = 0.0020$).

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Table 2. Summary of primary efficacy endpoint in the overall analysis

	TD (N = 100)	SD (N = 99)	P
Complete response duration, mean (SD)	13.39 (4.26)	10.89 (6.27)	0.0010
Occurrence of vomiting or rescue medication, n (%)	13 (13.0)	31 (31.3)	0.0019
Kaplan-Meier analysis			
Log-rank test	-	-	0.0013
Median (95% CI), days	Not estimable	Not estimable	-
P25 (95% CI)	Not estimable	2.89 (1.23-NE)	/
P75 (95% CI)	Not estimable	Not estimable	/

Note: NE = not estimable. The median CR duration could not be reliably estimated because fewer than 50% of patients in either group experienced a CR failure (vomiting or rescue medication) by the end of the 14-day observation period. The P25 could not be estimated in the TD group (event rate 13.0% < 25%), and the 75th percentile could not be estimated in either group (event rates < 75%). The 25th percentile for the SD group (event rate 31.3%) is presented as estimated. The log-rank test (P = 0.0013) compares the entire survival distributions and confirms a significant, sustained separation between the two groups (**Figure 2B**). Mean CR duration is reported as an alternative summary measure.

Table 3. Summary of complete response, complete control, and nausea control rate in the overall analysis

	TD (N=100)	SD (N = 99)	Statistic (χ^2)	P
Complete response rate, % (95% CI)				
Day 1	95.0 (92.16, 99.84)	83.8 (76.59, 91.09)	6.58	0.0104
Day 2-5	93.0 (88.00, 98.00)	74.7 (66.19, 83.31)	12.14	0.0005
Day 6-14	96.0 (92.16, 99.84)	90.9 (85.25, 96.57)	2.11	0.1462
Day 1-5	89.0 (82.87, 95.13)	69.7 (60.64, 78.75)	11.41	0.0008
Day 1-14	87.0 (80.41, 93.59)	68.7 (59.55, 77.82)	10.14	0.0019
Complete control rate, % (95% CI)				
Day 1	93.0 (88.00, 98.00)	75.8 (67.32, 84.20)	11.41	0.0008
Day 2-5	89.0 (82.87, 95.13)	69.7 (60.64, 78.75)	11.41	0.0008
Day 6-14	96.0 (92.16, 99.84)	86.9 (80.22, 93.52)	5.30	0.0212
Day 1-5	85.0 (78.00, 92.00)	61.6 (52.04, 71.20)	14.04	0.0002
Day 1-14	83.0 (75.64, 90.36)	59.6 (49.93, 69.26)	13.78	0.0003
Nausea control rate, % (95% CI)				
Day 1	95.0 (90.73, 99.27)	82.8 (75.40, 90.26)	7.47	0.0062
Day 2-5	91.0 (85.39, 96.61)	80.8 (73.05, 88.57)	4.29	0.0387
Day 6-14	98.0 (95.26, 100.00)	87.9 (81.45, 94.31)	7.76	0.0052
Day 1-5	89.0 (82.87, 95.13)	72.7 (63.95, 81.50)	8.50	0.0035
Day 1-14	88.0 (81.63, 94.37)	70.7 (61.74, 79.67)	9.92	0.0026

Note: Rates were compared using the Pearson Chi-square test or Fisher's exact test. χ^2 values are provided alongside the P-values.

Table 4. Rescue antiemetic administrations on Day 1, Days 2-5, and Days 6-14 following chemotherapy in the overall analysis

	TD (N = 100)	SD (N = 99)	P
Day 1	0.02 $\pm$ 0.14	0.03 $\pm$ 0.17	0.6465
Day 2-5	0.00 $\pm$ 0.00	0.02 $\pm$ 0.14	0.1562
Day 6-14	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	> 0.9999

Additionally, the TD group showed significantly longer durations of CC (14.64 $\pm$ 1.13 vs. 13.63

$\pm$ 2.63 days; P < 0.05) and nausea control (14.79 $\pm$ 0.76 vs. 13.95 $\pm$ 2.51 days; P < 0.05). Although rescue therapy administration frequency and time to first rescue use were numerically lower in the TD group, these differences did not achieve statistical significance (0.01 $\pm$ 0.09 vs. 0.07 $\pm$ 0.39; P > 0.05) (**Table 4**). The mean daily vomiting episode count was lower in the TD group across most assessment days, with statistically significant reductions observed on Day 1, 2, and 5 (P < 0.05)

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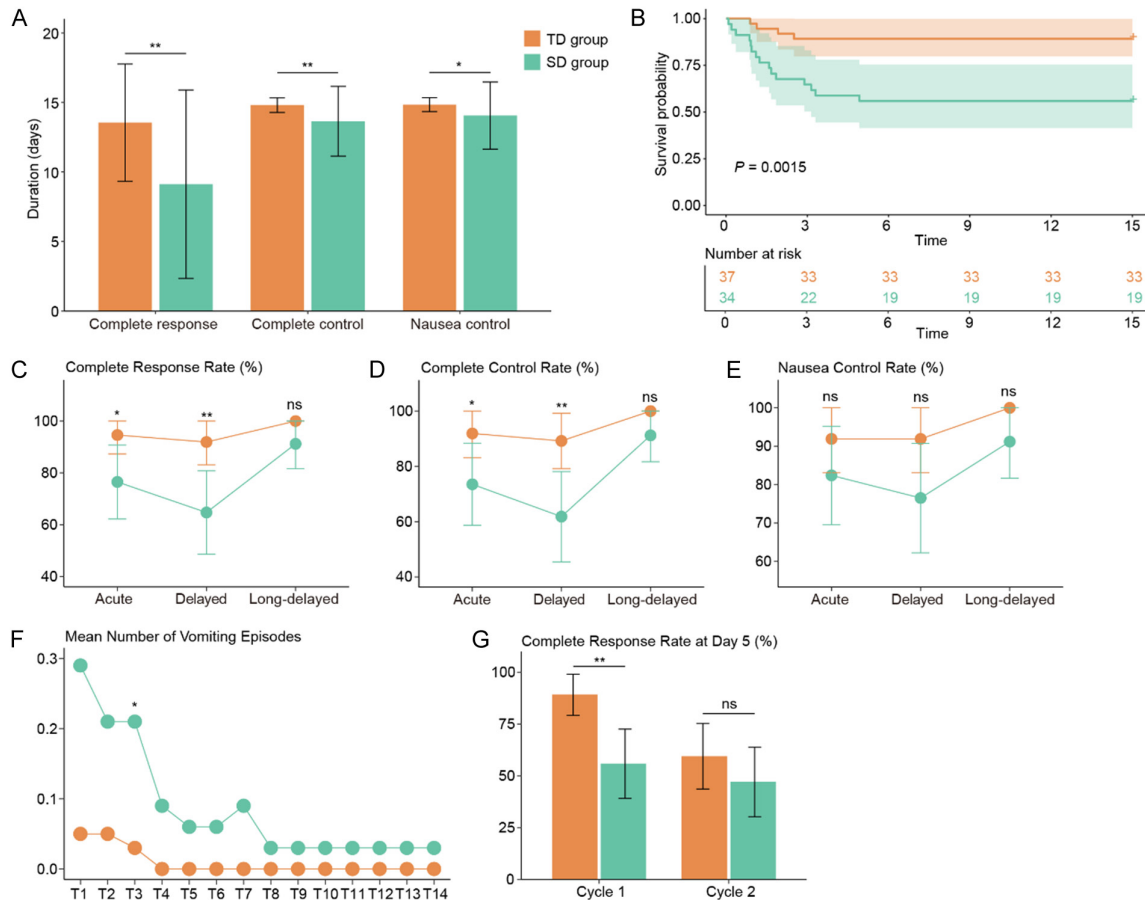


Figure 3. Primary and secondary efficacy endpoints in the multiday chemotherapy subgroup analysis. (A) Bar plots depicting the duration of complete response, complete control and nausea control between treatment groups. (B) Kaplan-Meier analysis of complete response duration between treatment groups. (C-E) Line graph illustrating complete response (C), complete control (D) and nausea control (E) rates at specified time points following chemotherapy. (F) Line graph depicting the mean daily number of vomiting episodes between treatment groups. (G) Bar plots showing the complete response rates at Day 5 across different chemotherapy cycles between treatment groups. Error bars represent 95% confidence intervals (CIs). Statistical significance is indicated as: ns, no significant difference; * $P < 0.05$; ** $P < 0.01$.

(Figure 2F). We did not observe any significant between-group differences in vomiting severity.

During the second chemotherapy cycle, both groups received the identical single-dose aprepitant regimen (130 mg on Day 1). The Day 5 CR rates were no longer significantly different between the two groups (59.5% vs. 47.1%; $P > 0.05$) (Figure 2G). This finding indicates that the superior CR rate observed in Cycle 1 was attributable to the two-dose regimen itself rather than baseline differences.

Subgroup analysis: patients receiving chemotherapy ≥ 3 days: Given that nearly half of

enrolled patients received multiday chemotherapy, a setting associated with greater cumulative emetogenic risk particularly during delayed and long-delayed phases. We therefore conducted a predefined subgroup analysis in patients undergoing chemotherapy lasting more than 3 days to assess whether the two-dose aprepitant regimen provided enhanced and sustained protection in this higher-risk population. In this predefined subgroup, the two-dose regimen demonstrated significant advantage across multiple efficacy endpoints. CR duration was significantly prolonged in the TD group compared with the SD group (13.55 ± 4.22 vs. 9.12 ± 6.78 days, $P < 0.05$) (Figure 3A, 3B).

Table 5. Summary of adverse events

	TD (N = 100)	SD (N = 99)	Statistic (χ^2)	P
AE, n (%)	25 (25.0)	24 (24.2)	0.01	0.9013
Drug-related AEs, n (%)	15 (15.0)	12 (12.1)	0.35	0.5532
Serious AEs, n (%)	0 (0)	0 (0)		/
Serious drug-related AEs, n (%)	0 (0)	0 (0)		/
Discontinuation due to AE, n (%)	0 (0)	0 (0)		/
Discontinuation due to drug-related AE, n (%)	0 (0)	0 (0)		/
Commonly reported AEs ($\geq 5\%$ of subjects)				
Decreased white blood cell count, n (%)	7 (7.0)	6 (6.1)	0.07	0.7886

Note: Adverse event incidences were compared using the Pearson Chi-square test or Fisher's exact test.

CR, CC, and nausea control rates were consistently higher in the TD group across all evaluated timepoints (**Figure 3C-E**), with statistically significant improvements observed during the acute and delayed phases.

The TD group also exhibited fewer vomiting episodes (significantly lower on Day 3) and delayed time to rescue therapy (0.02 ± 0.15 vs. 0.17 ± 0.65 days; $P > 0.05$) (**Figure 3F**). In Cycle 1, the TD group achieved a markedly higher Day 5 CR rate than the SD group (89.2% vs. 55.9%; $P < 0.01$) (**Figure 3G**), which underscores the importance of the Day 3 booster dose in countering the extended emetogenic peak associated with multiday chemotherapy.

Safety

A total of 49 patients (24.6%) experienced 50 adverse events (AEs), with 25 events in the TD group (25.0%) and 24 in the SD group (24.2%) ($P = 0.90$) (**Table 5**). Most AEs were Grade 1-2 in severity. The sole Grade 3 event was pain, occurring in one patient in the SD group (1.0%). No Grade ≥ 4 events were reported, and no patient discontinued treatment due to AEs.

The most common AE was decreased white blood cell count, which was attributed to chemotherapy rather than aprepitant regimen. No serious adverse events, treatment-related serious AEs, or injection site reactions (including erythema, swelling, or pain) were observed in either group, which highlights the tolerability of the aprepitant SME formulation.

Taken together, the two-dose regimen showed a safety profile similar to the single-dose regi-

men, with both well tolerated and associated with mainly mild-to-moderate AEs.

Discussion

Main findings and clinical implications

This randomized controlled trial shows that a TD aprepitant regimen offers superior and more sustained CINV protection than the single-dose one, with a comparable safety profile. The CR duration was significantly longer in the TD group, as confirmed by both descriptive statistics and Kaplan-Meier analysis. The TD regimen also outperformed across all phases in regard to secondary endpoints including CR, CC and nausea control, which highlights the clinical value of extended NK-1 receptor blockade. Our data supports the TD regimen as a new standard of care, particularly for those with high risk for prolonged or multiday CINV. Our results may inform updates to international antiemetic guidelines and ultimately benefit patient in various clinical settings.

The efficacy of the two-dose regimen was most evident in patients receiving multiday chemotherapy. The TD schedule greatly improved symptom control, reduced rescue therapy use, and lowered vomiting frequency in this population. The remarkable CR difference in Day 5 (89.2% vs. 55.9%) highlights the importance of risk-tailored antiemetic strategy in this subpopulation.

It is noteworthy that although the statistical significance was not achieved in some secondary endpoints in our study, the consistent and favorable trends observed in the TD group show a clinically meaningful advantage. Moreover, the TD regimen manifested a compa-

able safety profile with no obvious treatment-limiting AEs.

Taken together, these results support the TD aprepitant regimen as a more superior strategy for CINV, particularly in patients receiving multiday chemotherapy. These findings have practical values for refining supportive care protocols, minimizing patient discomfort, and improving chemotherapy adherence.

Comparison with previous studies

CINV control in delayed and long-delayed phases persists as a major clinical challenge. Multiple studies have explored the potential of extended antiemetic regimens to improve clinical outcomes. One study suggested that a 5-day aprepitant administration significantly reduced nausea (29.1% vs. 22.2%, $P = 0.0042$) and completely eliminated vomiting (6.7% vs. 0%, $P < 0.0001$) in the long-delayed phase [11]. In breast cancer patients receiving AC-based chemotherapy, a 6-day aprepitant dosing greatly reduced vomiting episodes and improved the full response rate (63% vs. 39%, $P < 0.001$) [12]. Similarly, a 7-day aprepitant regimen in patients undergoing high-dose chemotherapy reported fewer vomiting episodes [13]. These findings are coincident with a meta-analysis showing that a notable subset of patients suffer long-delayed CINV [5]. Nausea severity during this phase was comparable to delayed phase, underscoring the importance of sustained antiemetic coverage.

Our findings consolidate the observations in these reports and further support the concept of sustained NK-1RA blockade. Notably, here we modified the standard single-dose NK-1RA regimens to a two-dose aprepitant regimen in SME injectable formulation. By combination of pharmaceutical innovation with optimized dosing schedules, our strategy presents a candidate for future antiemetic guidelines.

Clinical benefits of extended regimen have also been reported in other NK-1RAs. A randomized trial showed that administration of fosaprepitant on days 1 and 3 significantly reduced nausea in delayed phase (6.17% vs. 12.66%; $P = 0.0056$) [14]. Consistently, Li et al. reported that two doses of fosaprepitant in patients receiving 3-day cisplatin resulted in

more CINV-free days and better life quality [9]. However, the triplet antiemetic prophylaxis showed only modest efficacy in non-small cell lung cancer patients receiving cisplatin-based HEC [15], which was likely due to insufficient regimens in certain high-risk populations. In BEAM-conditioned patients, NEPA plus dexamethasone provided robust protection in acute-phase control but nausea recurred on days 7-11 [16], highlighting the fundamental value of long-delayed phase management.

We also extend the follow-up beyond day 14 in this study to capture long-delayed CINV. In this regard, our work offers a more comprehensive view of symptom trajectories, which helps us to identify patients with persistent risk and provide a basis for risk-tailored prophylactic strategies. We further extended observation into the second chemotherapy cycle. These data further validate the superior efficacy of the TD aprepitant regimen. Notably, patients receiving multiday chemotherapy showed a more pronounced difference in CR duration (13.55 ± 4.22 vs. 9.12 ± 6.78 days, compared with 13.39 ± 4.26 vs. 10.89 ± 6.27 days overall), suggesting these patients may benefit more from TD regimen.

In summary, our inclusion of prolonged follow-up, second-cycle chemotherapy, and subgroup analyses offers novel insights into optimizing CINV control. The consistent advantage of TD regimen supports its potential in refining prophylactic protocol and individualizing risk-tailored supportive care.

Mechanistic considerations

First, aprepitant ($K_i = 0.12$ nM) has a better affinity for the human NK1 receptor than rolapitant ($K_i = 0.66$ nM) and netupitant ($K_i = 1.0$ nM) [17-19], which allows sustained receptor occupancy and prolonged antiemetic effects.

Second, we employ a novel SME formula for aprepitant administration. Preclinical studies have demonstrated that SME formulations enhance its apparent solubility and permeability, supporting sustained systemic exposure [20, 21]. The nanoscale size enables its stable dispersion and rapid IV delivery, while reduces the risk for injection-site reactions due to the lack of polysorbate surfactants.

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The combination of SME formula and high affinity of aprepitant guarantees the pharmacodynamic activity, safety and ease of use.

Quantitative PET has shown that both intravenous fosaprepitant (150 mg) and oral aprepitant (165 mg) achieve $\geq 97\%$ NK1 receptor occupancy (NK1RO) at 48 hours, which then declined to 37-76% and 41-75% by 120 hours, respectively [22]. This decline temporally coincides with the clinical onset of delayed and long-delayed CINV. The TD regimen is designed to maintain NK1RO $> 90\%$ throughout the entire phase, which is generally considered the threshold for effective emetic control [23].

In Cycle 1, CR rate at Day 5 was significantly higher in the TD group. In Cycle 2, CR rates declined and between-group difference was no longer significant when both groups were switched to the identical single-dose regimen ($P > 0.05$). This indicates that the superiority in Cycle 1 was likely attributable to the two-dose strategy rather than to baseline differences. Interestingly, participants previously receiving the TD regimen exhibited a lower incidence of CINV within 120 hours (4.0% vs. 10.1%). This may be a carryover effect, but the lack of statistical significance warrants cautious interpretation. On the other hand, uncontrolled CINV in the first cycle has been shown to increase the risk in the subsequent cycles [24]. Collectively, these findings underscore the importance of timely and sufficient prophylaxis offered by the two-dose regimen.

Of note, the dexamethasone dosage was different between groups on Days 3 and 4: the SD group received 3.75 mg BID, whereas the TD group received 3.75 mg QD. Despite lower corticosteroid exposure, the TD group achieved superior CINV control as the absolute between-group difference in delayed-phase CR (Days 2-5) was 18.3 percentage points (crude OR 4.49, 95% CI 1.81-11.14). The relative contribution of dexamethasone doses (8-20 mg/day on Days 2-4) to delayed CR was estimated to provide only a 4-7 percentage point improvement in a network meta-analysis [25]. Based on this, the differential corticosteroid exposure in our study explains at most 7 of the observed 18.3-point difference, leaving the majority of the effect attributable to the aprepitant regimen rather than dexamethasone. This finding suggests that extended NK-1RA

blockade is more effective over dexamethasone for delayed CINV, meanwhile avoiding the well-known side effects of prolonged corticosteroid use.

The safety profile of the highly receptor-specific NK-1RAs are well-defined [2]. The known adverse events such as fatigue, hiccups, mild gastrointestinal disturbances are generally dose- and duration-independent in our cohort. In addition, the polysorbate-free SME formulation used here minimizes local irritation while maintaining efficacy in contrast to earlier formulations such as fosaprepitant, an aprepitant prodrug containing polysorbate 80 which linked to injection site erythema [9]. No additive toxicity was observed when NK-1RAs were combined with corticosteroids. These findings confirm the overall safety of extended NK-1RA administration.

In summary, the two-dose aprepitant regimen provides sustained NK-1RA coverage across the entire phases, resulting in superior and durable CINV control. These findings support risk-tailored extension of antiemetic therapy.

Limitations and prospects

This study has several important limitations to be acknowledged. First, this was a single-center trial with a relative small sample size, which may limit the generalizability of our findings. Second, the open-label design may introduce potential assessment bias. Subjective measures such as nausea and vomiting are highly susceptible to this bias. We would like to emphasize that any potential bias would not favor the TD group, and this bias is mitigated by the concordance between subjective (e.g., CR rate, nausea control) and objective endpoints (vomiting episode count, time to first rescue). Third, the two groups differed in dexamethasone dosing and frequency (TD: QD on Days 2-4; SD: BID on Days 2-4). This confounder prevents the precise assessment of aprepitant regimen's effect. Nevertheless, the superior efficacy noticed in the TD group despite lower dexamethasone strongly supports the predominant role of the Day 3 aprepitant dose. Fourth, we lack molecular evidence, such as peripheral substance P levels or NK1 receptor expression, to directly support the mechanistic hypothesis of persistent and high receptor occupancy. Fifth, the Bonferroni or

FDR correction were not applied to the original multiple subgroup and multi-time-point comparisons, which may have inflated the risk of Type I errors. To address this, we reported BH-FDR adjusted *p*-values ($q = 0.05$) for all 15 secondary-endpoint comparisons ([Supplementary Table 1](#)), and the delayed-phase CR rate was pre-specified as the key secondary endpoint. Furthermore, the large effect sizes and low raw *P*-values make Type I error an unlikely explanation for the observed differences. Sixth, current follow-up covered only two chemotherapy cycles, which limits the assessment of efficacy and cumulative safety over long-term chemotherapy. Accordingly, a multi-center, double-blind, randomized, three-arm confirmatory trial has been designed to address these gaps and is currently under ethics committee review (anticipated submission Q4 2026). It has been designed to compare: (i) the TD submicron aprepitant regimen, (ii) the SD submicron aprepitant regimen, (iii) the SD regimen with dexamethasone matched to the TD schedule, with a planned enrollment of 600 HEC patients and a 6-cycle follow-up. The primary endpoint will be overall-phase CR rate.

Finally, various chemotherapy regimens among HEC patients prevented further stratified analyses in detail. Future studies should integrate patient-reported outcomes and molecular markers to refine subgroup evaluation. While our findings support the overall clinical benefits of the two-dose regimen, its simple dosing and safety profile make it highly amenable to inclusion into standardized supportive care and electronic medical order systems, a step for broader clinical application following confirmatory studies.

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Disclosure of conflict of interest

None.

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References

- [1] Kennedy SKF, Goodall S, Lee SF, DeAngelis C, Jocko A, Charbonneau F, Wang K, Pasetka M, Ko YJ, Wong HCY, Chan AW, Rajeswaran T, Gojsevic M, Chow E, Gralla RJ, Ng TL and Jerzak KJ. 2020 ASCO, 2023 NCCN, 2023 MASCC/ESMO, and 2019 CCO: a comparison of antiemetic guidelines for the treatment of chemotherapy-induced nausea and vomiting in cancer patients. *Support Care Cancer* 2024; 32: 280.
- [2] Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, Danso MA, Dennis K, Dupuis LL, Dusetzina SB, Eng C, Feyer PC, Jordan K, Noonan K, Sparacio D and Lyman GH. Antiemetics: ASCO guideline update. *J Clin Oncol* 2020; 38: 2782-2797.
- [3] Scotte F. Chemotherapy-induced nausea and vomiting: can we do better? *Curr Opin Oncol* 2025; 37: 158-162.
- [4] Berger MJ, Ettinger DS, Aston J, Barbour S, Bergsbaken J, Bierman PJ, Brandt D, Dolan DE, Ellis G, Kim EJ, Kirkegaard S, Kloth DD, Lagman R, Lim D, Loprinzi C, Ma CX, Maurer V, Michaud LB, Nabell LM, Noonan K, Roeland E, Rugo HS, Schwartzberg LS, Scullion B, Timoney J, Todaro B, Urba SG, Shead DA and Hughes M. NCCN guidelines insights: antiemesis, version 2.2017. *J Natl Compr Canc Netw* 2017; 15: 883-893.
- [5] Chow R, Yin LB, Baqri W, Huang R, Boldt G, Younus J, Lock M, Prsic E, Zimmermann C and Herrstedt J. Prevalence and predictors of long-delayed (> 120 h) chemotherapy-induced nausea and vomiting (CINV)-a systematic review and individual patient data meta-analysis. *Support Care Cancer* 2023; 31: 505.
- [6] Jordan K, de Azambuja E, Garcia Del Barrio MA, Jahn F, Di Palma M, Scotte F, Molassiotis A and Aapro M. Going beyond the 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. *Eur J Cancer* 2025; 222: 115451.
- [7] Grigio TR, Timmerman H, Dos Santos NP, Pereira JEG, Sousa AM and Wolff AP. Aprepitant and fosaprepitant as a prophylactic antiemetic for preventing postoperative nausea and vomiting after general anaesthesia: a systematic review and meta-analysis. *Clinics (Sao Paulo)* 2025; 80: 100783.
- [8] Sun Y, Zheng Y, Yang X, Xie K, Du C, He L, Gui Y, Fu J, Li C, Zhang H, Zhu L, Bie J, Sun Y, Fu Y, Zhou Y, Shou F, Wang Y and Zhu J. Incidence of

- chemotherapy-induced nausea and vomiting among cancer patients receiving moderately to highly emetogenic chemotherapy in cancer centers in Sichuan, China. *J Cancer Res Clin Oncol* 2021; 147: 2701-2708.
- [9] Li Y, Wan Y, Yang X, Chen P, Gui Y, He L, Xie Y, Tian J, Duan P, Liu G, Sun Y and Zhu J. Two doses of fosaprepitant included prophylactic treatment for the three-day cisplatin-based chemotherapy induced nausea and vomiting. *J Cancer Res Clin Oncol* 2024; 150: 290.
 - [10] Ottoboni T, Lauw M, Keller MR, Cravets M, Manhard K, Clendeninn N and Quart B. HTX-019 via 2-min injection or 30-min infusion in healthy subjects. *Future Oncol* 2019; 15: 865-874.
 - [11] Hayashi T, Shimokawa M, Matsuo K, Kawada K, Nakano T and Egawa T. Efficacy of 3-day versus 5-day aprepitant regimens for long-delayed chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based chemotherapy. *Expert Opin Pharmacother* 2023; 24: 2221-2226.
 - [12] Ahvazi NC, Hemati S and Mohamadianpanah M. Effect of increase in duration of aprepitant consumption from 3 to 6 days on the prevention of nausea and vomiting in women receiving combination of anthracycline/cyclophosphamide chemotherapy: a randomized, crossover, clinical trial. *Adv Biomed Res* 2015; 4: 238.
 - [13] Zhang M, Guo QL, Zhang TT, Fu M, Bi HT, Zhang JY and Zou KL. Efficacy and safety of Aprepitant-containing triple therapy for the prevention and treatment of chemotherapy-induced nausea and vomiting: a meta-analysis. *Medicine (Baltimore)* 2023; 102: e35952.
 - [14] Gao A, Guan S, Sun Y, Wang L, Meng F, Liu X, Gu L, Li G, Zhong D and Zhang L. Prolonged usage of fosaprepitant for prevention of delayed chemotherapy-induced nausea and vomiting(CINV) in patients receiving highly emetogenic chemotherapy. *BMC Cancer* 2023; 23: 609.
 - [15] Araz M, Beypinar I, Inci F, Koral L, Kocak MZ, Korkmaz M, Demirkiran A, Eryilmaz MK and Artac M. Comparison of granisetron and palonosetron in triplet anti-emetic prophylaxis in non-small cell lung cancer patients receiving cisplatin-based highly emetogenic chemotherapy. *J Oncol Pharm Pract* 2025; 31: 1241-1247.
 - [16] Bubalo JS, Radke JL, Bensch KG, Chen AI, Misra S and Maziarz RT. A phase II trial of netupitant/palonosetron for prevention of chemotherapy-induced nausea/vomiting in patients receiving BEAM prior to hematopoietic cell transplantation. *J Oncol Pharm Pract* 2024; 30: 304-312.
 - [17] Duffy RA, Morgan C, Naylor R, Higgins GA, Varty GB, Lachowicz JE and Parker EM. Rolapitant (SCH 619734): a potent, selective and orally active neurokinin NK1 receptor antagonist with centrally-mediated antiemetic effects in ferrets. *Pharmacol Biochem Behav* 2012; 102: 95-100.
 - [18] Rizzi A, Campi B, Camarda V, Molinari S, Cantoreggi S, Regoli D, Pietra C and Calo' G. In vitro and in vivo pharmacological characterization of the novel NK(1) receptor selective antagonist Netupitant. *Peptides* 2012; 37: 86-97.
 - [19] Huskey SE, Dean BJ, Bakhtiar R, Sanchez RI, Tattersall FD, Rycroft W, Hargreaves R, Watt AP, Chicchi GG, Keohane C, Hora DF and Chiu SH. Brain penetration of aprepitant, a substance P receptor antagonist, in ferrets. *Drug Metab Dispos* 2003; 31: 785-791.
 - [20] Angi R, Solymosi T, Otvos Z, Ordasi B, Glavinas H, Filipcsei G, Heltovics G and Darvas F. Novel continuous flow technology for the development of a nanostructured aprepitant formulation with improved pharmacokinetic properties. *Eur J Pharm Biopharm* 2014; 86: 361-368.
 - [21] Kalvakuntla S, Deshpande M, Attari Z and Kun-natur BK. Preparation and characterization of nanosuspension of aprepitant by H96 process. *Adv Pharm Bull* 2016; 6: 83-90.
 - [22] Van Laere K, De Hoon J, Bormans G, Koole M, Derdelinckx I, De Lepeleire I, Declercq R, Sanabria Bohorquez SM, Hamill T, Mozley PD, Tatosian D, Xie W, Liu Y, Liu F, Zappacosta P, Mahon C, Butterfield KL, Rosen LB, Murphy MG, Hargreaves RJ, Wagner JA and Shadle CR. Equivalent dynamic human brain NK1-receptor occupancy following single-dose i.v. fosaprepitant vs. oral aprepitant as assessed by PET imaging. *Clin Pharmacol Ther* 2012; 92: 243-250.
 - [23] Caberlotto L, Hurd YL, Murdock P, Wahlin JP, Melotto S, Corsi M and Carletti R. Neurokinin 1 receptor and relative abundance of the short and long isoforms in the human brain. *Eur J Neurosci* 2003; 17: 1736-1746.
 - [24] Fan J, Zhou Y, Bai G, Chu X, Di J and Yu L. Risk factors associated with anticipatory nausea and vomiting in children receiving chemotherapy: a cross-sectional study. *Support Care Cancer* 2025; 33: 979.
 - [25] Zhang Y, Yang Y, Zhang Z, Fang W, Kang S, Luo Y, Sheng J, Zhan J, Hong S, Huang Y, Zhou N, Zhao H and Zhang L. Neurokinin-1 receptor antagonist-based triple regimens in preventing chemotherapy-induced nausea and vomiting: a network meta-analysis. *J Natl Cancer Inst* 2017; 109: djw21.

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Supplementary Table 1. BH-FDR adjusted *p*-values for secondary endpoints in the overall analysis

Endpoint	Time	TD n/N	SD n/N	Raw P	BH-FDR P_adj	Significant (q = 0.05)
CR	Day 1	95/100	83/99	0.0104	0.0130	Yes
CR	Day 2-5	93/100	74/99	0.0005	0.0020	Yes
CR	Day 6-14	96/100	90/99	0.1462	0.1462	No
CR	Day 1-5	89/100	69/99	0.0008	0.0020	Yes
CR	Day 1-14	87/100	68/99	0.0019	0.0041	Yes
CC	Day 1	93/100	75/99	0.0008	0.0020	Yes
CC	Day 2-5	89/100	69/99	0.0008	0.0020	Yes
CC	Day 6-14	96/100	86/99	0.0212	0.0245	Yes
CC	Day 1-5	85/100	61/99	0.0002	0.0020	Yes
CC	Day 1-14	83/100	59/99	0.0003	0.0020	Yes
NC	Day 1	95/100	82/99	0.0062	0.0085	Yes
NC	Day 2-5	91/100	80/99	0.0387	0.0415	Yes
NC	Day 6-14	98/100	87/99	0.0052	0.0078	Yes
NC	Day 1-5	89/100	72/99	0.0035	0.0058	Yes
NC	Day 1-14	88/100	70/99	0.0026	0.0049	Yes

Notes: Of the 15 secondary-endpoint comparisons, 14 were significant at raw $P < 0.05$; all 14 survived BH-FDR correction at $q = 0.05$. The only comparison that did not reach significance (CR, Day 6-14) was non-significant at both raw ($P = 0.146$) and BH-FDR-adjusted ($P_{\text{BH-FDR}} = 0.146$) levels. The delayed-phase complete response rate (Day 2-5), pre-specified as the key secondary endpoint, remained highly significant after multiplicity adjustment ($P_{\text{BH-FDR}} = 0.0020$). Multiday chemotherapy subgroup analyses were also exploratory in nature and were not adjusted for multiplicity. The robustness of the most clinically important subgroup finding-Day 5 complete response rate (TD 89.2% vs. SD 55.9%, raw $P < 0.01$, absolute difference 33.3 percentage points)-is supported by the very large effect size, which makes Type I error inflation an implausible explanation. Method. Benjamini-Hochberg step-up procedure ($q = 0.05$). The 15 tests comprise the 3 secondary endpoints (complete response, complete control, nausea control) $\times$ 5 time intervals (Day 1, Day 2-5, Day 6-14, Day 1-5, Day 1-14) pre-specified in the study protocol. All 15 tests are treated as a single family for multiplicity control.