

Recent developments in the clinical pharmacology of rolapitant: subanalyses in specific populations

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Abstract: Knowledge of the involvement of the neurokinin substance P in emesis has led to the development of the neurokinin-1 receptor antagonists (NK-1 RAs) for control of chemotherapy-induced nausea and vomiting (CINV), in combination with serotonin type 3 receptor antagonists and corticosteroids. The NK-1 RA rolapitant, recently approved in oral formulation, has nanomolar affinity for the NK-1 receptor, as do the other commercially available NK-1 RAs, aprepitant and netupitant. Rolapitant is rapidly absorbed and has a long half-life in comparison to aprepitant and netupitant. All three NK-1 RAs undergo metabolism by cytochrome P450 (CYP) 3A4, necessitating caution with the concomitant use of CYP3A4 inhibitors, but in contrast to aprepitant and netupitant, rolapitant does not inhibit or induce CYP3A4. However, rolapitant is a moderate inhibitor of CYP2D6, and concomitant use with CYP2D6 substrates with narrow therapeutic indices should be avoided. Aprepitant, netupitant, and rolapitant have all demonstrated efficacy in the control of delayed CINV in patients receiving moderately and highly emetogenic chemotherapy in randomized controlled trials, including over multiple cycles of chemotherapy. We reviewed recent post hoc analyses of clinical trial data demonstrating that rolapitant is efficacious in the control of CINV in patient populations with specific tumor types, namely, breast cancers, gastrointestinal/colorectal cancers, and lung cancers. In addition, we show that rolapitant has efficacy in the control of CINV in specific age groups of patients receiving chemotherapy (<65 and ≥65 years of age). Overall, the safety profile of rolapitant in these specific patient populations was consistent with that observed in primary analyses of phase 3 trials.

Keywords: rolapitant, neurokinin-1 receptor antagonist, chemotherapy-induced nausea and vomiting, post hoc analyses

Introduction to the management of chemotherapy-induced nausea and vomiting (CINV)

Nausea and vomiting are the side effects most feared by patients undergoing cytotoxic chemotherapies.¹⁻³ The 5-day at-risk period for CINV typically manifests in two distinct phases. The acute phase, which occurs during the first 24 hours after chemotherapy, is largely mediated by free radical-induced serotonin (5-hydroxytryptamine [5-HT]) release in the small intestine and consequent activation of 5-HT type 3 (5-HT₃) receptors located on vagal terminals in the gut wall.⁴⁻⁶ The delayed phase of CINV starts on day 2 after chemotherapy, can last until day 5, and is predominantly mediated by a central pathway that involves binding of the mammalian tachykinin family neurotransmitter/neuromodulator, substance P, to neurokinin-1 (NK-1) receptors located in the brainstem.^{4,5,7}

CINV in the acute phase is reasonably well-managed in the majority of patients by 5-HT₃ receptor antagonists, such as palonosetron, which also has activity in the

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delayed phase.^{8,9} However, full control of delayed-phase CINV still presents a treatment challenge.

Other medications have also been used in the treatment of CINV. Corticosteroids such as dexamethasone are used in combination with 5-HT₃ antagonists for the control of acute CINV, and either alone or in combination with NK-1 receptor antagonists for control of delayed CINV,^{10–13} although their mechanism of action is not well understood.¹⁴ Dopamine type 2 receptors are present in the brainstem nuclei involved in triggering emesis; the earliest agents used in control of emesis were dopamine antagonists such as the phenothiazines (chlorpromazine) and butyrophenones (haloperidol). However, extrapyramidal symptoms and other adverse effects have limited the use of these agents;^{5,15} expert opinion and current National Comprehensive Cancer Network guidelines recommend the use of dopamine antagonists such as haloperidol or metoclopramide in the treatment of established and breakthrough nausea and emesis.^{5,12} The atypical antipsychotic olanzapine has antagonistic actions at a range of dopamine and serotonin receptors, including dopamine type 2 and 5-HT₃ receptors, and in a recent trial it was shown to be superior to placebo when added to a combination of a 5-HT₃ antagonist, dexamethasone, and an NK-1 receptor antagonist for the complete control of nausea (defined as a response of 0 on a visual analog scale [VAS] with a maximum of 10). In patients receiving highly emetogenic chemotherapy (HEC), the percentage with no nausea (response of 0 on the VAS) significantly improved compared with control in the acute phase (74% vs 45%; $P=0.002$), delayed phase (42% vs 25%; $P=0.002$), and overall phase (days 1 to 5) (37% vs 22%; $P=0.002$); the proportions of patients with complete responses were also superior after olanzapine-containing regimens vs placebo in the acute (86% vs 65%; $P<0.001$), delayed (67% vs 52%; $P=0.007$), and overall phases (64% vs 41%; $P<0.001$).¹⁶ Current Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology guidelines recommend the use of olanzapine for breakthrough nausea and emesis and as first-line prophylaxis for HEC.¹³

Advances in the understanding of the role played by substance P in emesis has led to the investigation and development of NK-1 receptor antagonists for the control of delayed-phase CINV. Aprepitant was the first oral NK-1 antagonist to be approved, in 2003, and was followed by fosaprepitant, a pro-drug of aprepitant in an intravenous (IV) formulation, and netupitant, formulated as a fixed oral combination with palonosetron; casopitant was not approved. Rolapitant has been recently approved in an oral formulation and is currently under US Food and Drug Administration

(FDA) review in a bioequivalent IV formulation.¹⁷ Herein we review the clinical pharmacology and efficacy of rolapitant in the context of the other NK-1 receptor antagonists, as well as the clinical efficacy of rolapitant in subpopulations of chemotherapy patients with specific tumor types.

Clinical pharmacology of NK-1 receptor antagonists

NK-1 receptor affinity and occupancy

In vitro studies have shown that rolapitant binds with high affinity to the human NK-1 receptor (K_i , 0.66 nmol/L) and has >1,000-fold selectivity for the NK-1 receptor vs NK-2 and NK-3 receptor subtypes.¹⁸ The affinity of netupitant at the human NK-1 receptor is also in the nanomolar range (1.0 nmol/L),¹⁹ while aprepitant displaces 50% of substance P from human NK-1 receptors at a concentration of 0.12 nmol/L.²⁰ Positron emission tomography (PET) data have shown that plasma concentrations of rolapitant of 348 ng/mL correspond to >90% NK-1 receptor occupancy, and that such plasma concentrations are observed with the recommended 180 mg dose of oral rolapitant.²¹ Receptor occupancy levels >90% were also achieved with 300 mg oral netupitant, 125 mg oral aprepitant, and 150 mg IV fosaprepitant in PET studies.^{22–25} This level of occupancy was maintained 96 hours after administration of netupitant²⁴ and 120 hours after administration of rolapitant,²¹ suggesting that a single dose of either of these two compounds would provide protective efficacy against delayed-phase CINV. However, it has been predicted that a single 125 mg dose of oral aprepitant will maintain >90% receptor occupancy for 24 hours only, necessitating further dosing (at 80 mg/day) on days 2 and 3 post-chemotherapy.²²

Pharmacokinetic properties of NK-1 receptor antagonists

Rolapitant is rapidly absorbed in healthy individuals, with its mean peak plasma concentration reaching 968 ng/mL 4 hours following a single 180 mg oral dose, and has a bioavailability of approximately 100%.^{26,27} Administration of aprepitant, fosaprepitant, and netupitant to healthy volunteers resulted in mean peak plasma concentrations of 1,539 ng/mL (4 hours after 125 mg dose on day 1) to 1,356 ng/mL (4 hours after 80 mg dose on day 3), 4,200 ng/mL (aprepitant concentration within 30 minutes of 150 mg IV infusion of fosaprepitant), and 434 ng/mL (5 hours after 300 mg dose), respectively, with bioavailabilities of at least 59%.^{28–32} The half-life of rolapitant is 169–183 hours,²⁶ substantially longer than that of aprepitant (9–13 hours following either oral

aprepitant or IV fosaprepitant)^{29,30} or netupitant (80 hours in cancer patients).^{24,28}

Rolapitant is metabolized primarily by cytochrome P450 (CYP) 3A4, forming the active metabolite M19, and chronic concomitant use of strong inducers of CYP3A4 should therefore be avoided;²⁶ conversely, neither rolapitant nor M19 has any inductive or inhibitory effect on CYP3A4.³³ Oral rolapitant inhibits the breast cancer resistance protein transporter and the P-glycoprotein transporter and moderately inhibits CYP2D6. Monitoring for adverse events is recommended if concomitant use with substrates of breast cancer resistance protein, P-glycoprotein, or CYP2D6 with narrow therapeutic windows cannot be avoided; concomitant use of the CYP2D6 substrate pimozide should be avoided and concomitant use with thioridazine is contraindicated.²⁶ It should be noted that rolapitant in IV formulation does not significantly inhibit the breast cancer resistance protein transporter nor the P-glycoprotein transporter.³⁴

Aprepitant is metabolized primarily by CYP3A4, as well as by CYP1A2 and CYP2C19; caution should be used regarding concomitant administration of CYP3A4 inhibitors, and strong inducers of this enzyme should be avoided.^{29,35} In addition, aprepitant is both a weak to moderate dose-dependent inhibitor and weak inducer of CYP3A4, and also an inducer of CYP2C9; hence, concomitant use of benzodiazepines, chemotherapeutic substrates of CYP3A4, and CYP2C9 substrates (such as warfarin) should be carefully monitored. Dose reductions in corticosteroids (dexamethasone) are necessary and may be necessary when coadministering benzodiazepines, depending on the clinical situation.^{29,36–38}

Netupitant is metabolized by and acts as a moderate inhibitor of CYP3A4, and increases exposure to CYP3A4 substrates midazolam, erythromycin, and dexamethasone. Dose reductions in dexamethasone are required, and may be necessary when coadministering other CYP3A4 substrates; caution and adverse event monitoring is recommended in patients receiving chemotherapeutic substrates of CYP3A4. Use of strong CYP3A4 inducers with netupitant should be avoided.^{28,39}

Clinical efficacy of NK-1 receptor antagonists

Aprepitant/fosaprepitant and netupitant

The efficacy of NK-1 receptor antagonists for prevention of delayed CINV when used in combination with a 5-HT₃ receptor antagonist and a corticosteroid has been established in a number of randomized controlled trials; these trials were conducted by comparison of the addition of the

respective NK-1 receptor antagonist to a 5HT₃ antagonist/corticosteroid combination vs the addition of placebo to the same combination (active control). When using the proportion of patients with a complete response (no emesis and no use of rescue medication) in the delayed phase of cycle 1 of chemotherapy treatment as an endpoint, aprepitant was superior to active control in two studies that enrolled patients receiving cisplatin-based HEC (75% vs 56% and 68% vs 47% in each study, respectively; $P < 0.001$ for both comparisons),^{40,41} and in two studies that enrolled patients receiving moderately emetogenic chemotherapy (MEC) or doxorubicin/cyclophosphamide-based chemotherapy (67% vs 32%; $P < 0.05$ and 71% vs 61%; $P < 0.01$, respectively).^{42,43} Fosaprepitant was shown to be superior to active control for the same endpoint measure in patients receiving cisplatin-based HEC (65% vs 49%; $P = 0.0025$)⁴⁴ and MEC (79% vs 69%; $P < 0.001$),⁴⁵ and non-inferiority to aprepitant was also demonstrated (fosaprepitant vs aprepitant, 74% vs 74%).⁴⁶ Netupitant (administered in combination with palonosetron) was also superior to active control for complete response during the delayed phase of cycle 1 in patients receiving anthracycline and cyclophosphamide (AC)-based chemotherapy (77% vs 70%; $P = 0.001$),⁴⁷ and in patients receiving cisplatin-based chemotherapy (90% vs 80%; $P < 0.05$).⁴⁸

Rolapitant

All trials evaluating efficacy have been performed with oral rolapitant; however, the IV formulation has been shown to be bioequivalent¹⁷ and is currently under review by the FDA. Complete response rates during the acute, delayed, and overall phases of the first cycle of HEC and MEC in trials of rolapitant are shown in Table 1. Rolapitant was superior to active control for complete response rates in the delayed and overall phases of two trials that enrolled patients receiving HEC,⁴⁹ and one trial that enrolled patients receiving MEC or AC-based regimens.⁵⁰ Complete response rates in the acute phase were also superior in patients receiving rolapitant vs active control after administration of HEC, but not MEC/AC. The benefit of rolapitant is also sustained over multiple cycles of chemotherapy in patients receiving HEC or MEC/AC, as demonstrated in a pooled analysis of these trials.⁵¹

Clinical efficacy of rolapitant – subanalyses in specific populations

Tumor types – breast, gastrointestinal (GI)/colorectal, and lung cancers

To evaluate the efficacy and safety of rolapitant in various tumor types, post hoc analyses have recently been carried out

Table 1 Complete response (%) in total population by phase and chemotherapy treatment following oral administration of rolapitant

	MEC or AC trial, % ⁵⁰	P-value	HEC1 and HEC2 trials; cisplatin-based, % ⁴⁹	P-value
	ROL (n=666) vs CON (n=666)		ROL (n=535) vs CON (n=535)	
Acute phase (0–24 h)	83.5 vs 80.3	0.1425	83.6 vs 76.6	0.0045
Delayed phase (24–120 h)	71.3 vs 61.6	0.0002	71.4 vs 60.2	0.0001
Overall phase (0–120 h)	68.6 vs 57.8	<0.0001	68.8 vs 58.5	0.0005

Abbreviations: AC, anthracycline and cyclophosphamide; CON, control; h, hours; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; ROL, rolapitant.

on clinical trial data from patients receiving chemotherapy for breast cancers, GI and colorectal cancers, and lung cancers. In breast cancer patients who were enrolled in the phase 3 trial of rolapitant for CINV induced by MEC or AC-based regimens,⁵⁰ complete response rates were greater with rolapitant than with active control in the overall (62.8% vs 55.1%; $P=0.023$) and delayed phases (66.7% vs 59.8%; $P=0.039$) (Table 2), as were no emesis rates, although no significant differences were observed in the endpoints of no nausea (Table 3) or no significant nausea.⁵² As 80% of this group of patients received AC-based chemotherapy, analyses were also carried out on just those patients receiving AC-based regimens, and similar findings to the overall breast cancer population regarding the endpoints of complete response (Table 2), no nausea (Table 3), and no significant nausea were reported.

Patients who enrolled in three previous trials of rolapitant who were receiving chemotherapy for GI or colorectal cancer were included in two post hoc analyses. Data were pooled from the two trials of patients who received cisplatin-based HEC for the first analysis,⁴⁹ and complete response rates were significantly higher in patients who received rolapitant compared to active control in the delayed (72.2% vs 48.0%; $P=0.012$) and overall phases (72.2% vs 48.0%; $P=0.012$) (Table 2).⁵³ For the endpoint of no emesis, rolapitant was superior to active control in both the delayed and overall phases, and was also superior in the overall (but not delayed) phase for the endpoint of no nausea (Table 3). For the second analysis, data were drawn from the trial of rolapitant in patients who received MEC or AC-based chemotherapies,⁵⁰ but only those patients who received MEC were included; the most commonly used non-AC agents were irinotecan (rolapitant, 68.1% of patients; placebo, 70.3% of patients) and oxaliplatin (27.7% and 21.6% of patients, respectively). Complete response rates were higher in the acute (91.5% vs 73.0%; $P=0.025$) (Tesar, Inc., data on file, 2016) and overall phases (74.5% vs 48.6%; $P=0.016$) of CINV in patients receiving rolapitant, and numerically but not significantly higher in the delayed phase (74.5% vs 54.1%; $P=0.052$) (Table 2).⁵³ Rates of no nausea were significantly

higher in patients receiving rolapitant in the delayed and overall phases (Table 3), while rates of no emesis were higher in both the delayed and overall phases but in neither phase was this difference significant.

For analysis of rolapitant benefits in patients receiving chemotherapy for lung cancer, data were pooled from the same three previous trials.^{49,50} The majority of patients received cisplatin (rolapitant, 70.0% of patients; placebo, 65.7% of patients) while almost all of the remaining patients received carboplatin (29.4% and 32.6% of patients, respectively). Rolapitant significantly improved complete response rates compared to active control in the acute (88.4% vs 81.7%; $P=0.014$), delayed (77.4% vs 65.1%; $P<0.001$), and overall phases (75.4% vs 63.1%; $P<0.001$) of CINV in these patients (Table 2); no emesis rates were also improved in all phases, while no nausea rates were improved in the delayed and overall, but not acute phases (Table 3).⁵⁴

Elderly patients

To investigate the efficacy of rolapitant in elderly and younger patients, data were drawn from the three previous trials of rolapitant, and were stratified based on patient age (<65 years vs ≥ 65 years) and type of chemotherapy (HEC vs MEC or AC-based chemotherapy).^{49,50} The majority of patients receiving cisplatin-based HEC in both age groups were male (<65 years: rolapitant, 59.9% and active control, 63.1%; ≥ 65 years, rolapitant, 71.7% and active control, 62.0%), whereas male patients were the minority of those who received MEC or AC-based chemotherapy (<65 years: rolapitant, 14.7% and active control, 12.1%; ≥ 65 years: rolapitant, 36.3% and active control, 37.2%). The median ages of patients in the age <65 years stratification from each treatment arm of each of the HEC and MEC studies ranged from 52 to 56 years, with the youngest patient included aged 18 years. In this younger age group, complete response rates were superior in the delayed and overall phases in patients receiving rolapitant, both after cisplatin-based HEC (delayed: 71.3% vs 59.8%; $P<0.001$; overall: 68.0 vs 58.5%; $P=0.006$) and MEC/AC-based regimens (delayed: 70.3% vs 60.9%;

Table 2 Complete response (%) by cancer population, phase, and chemotherapy treatment following oral administration of rolapitant

	Breast cancer population ⁵²			GI/colorectal cancer population ^{53,*}			Lung cancer population ⁵⁴		
	MEC plus AC, %	P-value	AC only, %	MEC; non-AC, %	P-value	Cisplatin-based ^a , %	P-value	Carboplatin or cisplatin-based ^b , %	P-value
	ROL (n=417) vs CON (n=428)		ROL (n=333) vs CON (n=347)	ROL (n=47) vs CON (n=37)		ROL (n=54) vs CON (n=50)		ROL (n=337) vs CON (n=350)	
Acute phase (0–24 h)	77.9 vs 77.8	0.963	76.0 vs 76.7	91.5 vs 73.0	0.835	88.9 vs 80.0	0.212	88.4 vs 81.7	0.014
Delayed phase (24–120 h)	66.7 vs 59.8	0.039	66.7 vs 58.8	74.5 vs 54.1	0.034	72.2 vs 48.0	0.012	77.4 vs 65.1	<0.001
Overall phase (0–120 h)	62.8 vs 55.1	0.023	62.5 vs 53.9	74.5 vs 48.6	0.024	72.2 vs 48.0	0.012	75.4 vs 63.1	<0.001

Notes: *Pooled analysis of the two HEC phase 3 trials; ^bpooled analysis of the two HEC and the MEC plus AC trials. *(Tesaro, Inc., data on file, 2016).

Abbreviations: AC, anthracycline and cyclophosphamide; CON, control; GI, gastrointestinal; h, hours; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; ROL, rolapitant.

Table 3 Endpoint of no nausea (%) by cancer population, phase, and chemotherapy treatment following oral administration of rolapitant

	Breast cancer population ⁵²			GI/colorectal cancer population ^{53,*}			Lung cancer population ⁵⁴		
	MEC plus AC, %	P-value	AC only, %	MEC; non-AC, %	P-value	Cisplatin-based ^a , %	P-value	Carboplatin or cisplatin-based ^b , %	P-value
	ROL (n=417) vs CON (n=428)		ROL (n=333) vs CON (n=347)	ROL (n=47) vs CON (n=37)		ROL (n=54) vs CON (n=50)		ROL (n=337) vs CON (n=350)	
Acute phase (0–24 h)	56.8 vs 62.1	0.116	54.1 vs 59.1	74.5 vs 56.8	0.187	75.9 vs 58.0	0.053	75.7 vs 70.9	0.155
Delayed phase (24–120 h)	38.8 vs 40.4	0.641	36.9 vs 38.9	61.7 vs 35.1	0.597	48.1 vs 30.0	0.060	63.5 vs 51.1	0.001
Overall phase (0–120 h)	35.3 vs 37.4	0.520	33.6 vs 35.2	57.4 vs 35.1	0.676	48.1 vs 28.0	0.036	60.5 vs 48.6	0.002

Notes: *Pooled analysis of the two HEC phase 3 trials; ^bpooled analysis of the two HEC and the MEC plus AC trials. *(Tesaro, Inc., data on file, 2016).

Abbreviations: AC, anthracycline and cyclophosphamide; CON, control; GI, gastrointestinal; h, hours; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; ROL, rolapitant.

Table 4 Complete response (%) by age, phase, and chemotherapy treatment following oral administration of rolapitant^{55,56}

	Patients <65 years old				Patients ≥65 years old			
	MEC plus AC, %		Cisplatin-based ^a , %		MEC- or AC-based, %		Cisplatin-based ^a , %	
	ROL (n=495) vs CON (n=470)	P-value	ROL (n=397) vs CON (n=393)	P-value	ROL (n=171) vs CON (n=196)	P-value	ROL (n=138) vs CON (n=142)	P-value
Acute phase (0–24 h)	81.8 vs 77.9	0.127	81.9 vs 76.8	0.082	88.3 vs 86.2	0.553	88.4 vs 76.1	0.007
Delayed phase (24–120 h)	70.3 vs 60.9	0.002	71.3 vs 59.8	<0.001	74.3 vs 63.3	0.024	71.7 vs 61.3	0.064
Overall phase (0–120 h)	67.5 vs 56.6	<0.001	68.0 vs 58.5	0.006	71.9 vs 60.7	0.024	71.0 vs 58.5	0.028

Note: ^aPooled analysis of the two HEC phase 3 trials.

Abbreviations: AC, anthracycline and cyclophosphamide; CON, control; h, hours; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; ROL, rolapitant.

$P=0.002$; overall: 67.5% vs 56.6%; $P<0.001$) (Table 4).^{55,56} For the endpoints of no emesis and no nausea (Table 5), rolapitant was superior in the younger age group for the delayed and overall phases in patients who received cisplatin-based HEC; rolapitant was also superior for no emesis in the delayed and overall phases for MEC/AC-treated patients, but not for the endpoint of no nausea.⁵⁶

The median ages of patients in the age ≥ 65 years stratification from each treatment arm of each of the HEC and MEC studies ranged from 68 to 70 years, with the oldest patient included aged 90 years. Patients in this older age group who had received cisplatin-based HEC had complete response rates that were higher in the acute (88.4% vs 76.1%; $P=0.007$) and overall phases (71.0% vs 58.5%; $P=0.028$), while higher rates observed in the delayed phase were not statistically significant (71.7% vs 61.3%; $P=0.064$) (Table 4).^{55,56} However, in older patients who received MEC or AC-based regimens, complete response rates were higher for rolapitant in the delayed (74.3% vs 63.3%; $P=0.024$) and overall (71.9% vs 60.7%; $P=0.024$), but not the acute phases (88.3% vs 86.2%; $P=0.553$). In this age group, patients who received cisplatin-based HEC showed improved rates of no emesis after rolapitant in all CINV phases, and improved rates of no nausea in the acute phase (Table 5); in older patients who received MEC or AC-based regimens, greater rates of

no emesis were observed in the delayed and overall phases, while no effect of rolapitant was observed for the endpoint of no nausea.⁵⁶

Conclusion

In post hoc analyses, rolapitant has shown superiority over active control for prevention of CINV over the full 5-day at-risk period in patient populations receiving HEC and MEC specifically for breast, GI/colorectal, and lung cancers, and in populations stratified by age (<65 and ≥ 65 years). For delayed-phase CINV, rolapitant was also superior to active placebo in these specific populations, although not to statistical significance in patients receiving non-AC MEC regimens for GI/colorectal cancers nor in patients aged ≥ 65 years receiving cisplatin-based HEC regimens. These results are consistent with the findings of the overall phase 3 clinical trials, and provide additional information about the potential therapeutic utility of rolapitant in specific populations. In the post hoc analyses, the incidence of adverse events was generally similar in the rolapitant and placebo arms, and the safety profile of rolapitant was consistent with the safety data from the primary analysis of the phase 3 trials. It should be noted that oral netupitant with palonosetron and oral aprepitant are FDA-approved alternative NK-1 receptor antagonists for control of CINV.

Table 5 Endpoint of no nausea (%) by age, phase, and chemotherapy treatment following oral administration of rolapitant^{55,56}

	Patients <65 years old				Patients ≥65 years old			
	MEC plus AC, %		Cisplatin-based ^a , %		MEC plus AC, %		Cisplatin-based ^a , %	
	ROL (n=495) vs CON (n=470)	P-value	ROL (n=397) vs CON (n=393)	P-value	ROL (n=171) vs CON (n=196)	P-value	ROL (n=138) vs CON (n=142)	P-value
Acute phase (0–24 h)	60.4 vs 61.9	0.630	67.3 vs 62.8	0.194	78.4 vs 75.5	0.519	79.7 vs 68.3	0.030
Delayed phase (24–120 h)	44.6 vs 42.1	0.430	54.7 vs 42.5	<0.001	59.6 vs 51.5	0.119	58.7 vs 49.3	0.115
Overall phase (0–120 h)	41.2 vs 38.5	0.392	50.9 vs 39.9	0.002	57.9 vs 50.5	0.157	56.5 vs 46.5	0.093

Note: ^aPooled analysis of the two HEC phase 3 trials.

Abbreviations: AC, anthracycline and cyclophosphamide; CON, control; h, hours; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; ROL, rolapitant.

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