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Single-dose aprepitant *vs* ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind Phase III trial in patients undergoing open abdominal surgery†

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Background. The neurokinin$_1$ antagonist aprepitant is effective for prevention of chemotherapy-induced nausea and vomiting. We compared aprepitant with ondansetron for prevention of post-operative nausea and vomiting.

Methods. Nine hundred and twenty-two patients receiving general anaesthesia for major abdominal surgery were assigned to receive a single preoperative dose of oral aprepitant 40 mg, oral aprepitant 125 mg, or i.v. ondansetron 4 mg in a randomized, double-blind trial. Vomiting episodes, use of rescue therapy, and nausea severity (verbal rating scale) were documented for 48 h after surgery. Primary efficacy endpoints were complete response (no vomiting and no use of rescue therapy) 0–24 h after surgery and no vomiting 0–24 h after surgery. The secondary endpoint was no vomiting 0–48 h after surgery.

Results. Aprepitant at both doses was non-inferior to ondansetron for complete response 0–24 h after surgery (64% for aprepitant 40 mg, 63% for aprepitant 125 mg, and 55% for ondansetron, lower bound of 1-sided 95% CI$>$0.65), superior to ondansetron for no vomiting 0–24 h after surgery (84% for aprepitant 40 mg, 86% for aprepitant 125 mg, and 71% for ondansetron; $P<0.001$), and superior for no vomiting 0–48 h after surgery (82% for aprepitant, 40 mg, 85% for aprepitant, 125 mg, and 66% for ondansetron; $P<0.001$). The distribution of peak nausea scores was lower in both aprepitant groups *vs* ondansetron ($P<0.05$).

Conclusions. Aprepitant was non-inferior to ondansetron in achieving complete response for 24 h after surgery. Aprepitant was significantly more effective than ondansetron for preventing vomiting at 24 and 48 h after surgery, and in reducing nausea severity in the first 48 h after surgery. Aprepitant was generally well tolerated.

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Nausea and vomiting occur in as many as 70–80% of patients in the first 24 h after surgery.[1–5] Even among patients who receive antiemetic prophylaxis with i.v. $5HT_3$ receptor antagonists (RAs) or other drugs, 30–40% still experience postoperative nausea and vomiting (PONV).[6] Thus, an unmet medical need for improved PONV prophylaxis exists. A new class of drug known as non-peptide neurokinin$_1$ (NK_1) RAs has demonstrated activity against both peripheral and central emetic stimuli in animal models.[7–9] Consistent with the idea that antagonism at the NK_1 receptor could affect the response to emetic stimuli,[10–13] evidence suggesting the potential efficacy of NK_1 RAs against PONV was obtained in clinical trials of two different drugs in this class, which were assessed in patients undergoing major gynaecological surgery.[14] In one study, a significantly lower incidence of vomiting in the first 24 h after surgery was observed with an NK_1 RA given either alone or in combination with a $5HT_3$ RA, compared with the $5HT_3$ RA alone.[15] In another study, an NK_1 RA given to patients with established PONV was superior to placebo in controlling vomiting.[16]

Aprepitant, a highly selective, brain-penetrant NK_1 RA with a long half-life and preclinical efficacy against opioid-induced emesis,[7 9 17] has demonstrated efficacy against chemotherapy-induced nausea and vomiting when combined with other antiemetics, and is the first in its class to be approved for this indication.[17] To examine the possibility that it may also provide benefit against PONV, an initial Phase IIb/III study of aprepitant *vs* the $5HT_3$ RA ondansetron was conducted in patients undergoing open abdominal surgery.[18] In that study, which was the first trial of aprepitant for prevention of PONV, the treatments showed similar efficacy for the primary endpoint of complete response (no vomiting and no use of rescue), but aprepitant provided greater protection against vomiting during the first 24 and 48 h after surgery. The present study was conducted to confirm these positive results in an international population, more thoroughly assess the clinical profile of aprepitant by comparing it with ondansetron for no vomiting and other endpoints, and to define better the apparent similarity for complete response seen in the first study comparing aprepitant and ondansetron.

Methods

A total of 42 centres (eight U.S. sites and 34 non-U.S. sites in North America, South America, Europe, Australia, and Asia) participated in this randomized double-blind study (Protocol 091) between May 28, 2004 and April 20, 2005. Approval from the Institutional Review Board for each centre was obtained and all patients gave written informed consent.

Patients

Patients, aged ≥18 yr old, ASA I–III, undergoing open abdominal surgery requiring at least one overnight hospital stay and receiving volatile-agent-based general anaesthesia including nitrous oxide were enrolled. Among exclusion criteria were pregnancy/breastfeeding status, need for a nasogastric or oral-gastric tube, use of neuroaxial- or propofol-maintained anaesthesia, vomiting within 24 h before surgery or of any organic aetiology, allergy to any medications to be used before operation or intra-operatively, pre-established need for intensive care or step-down unit care after operation, evidence of disease or history of illness which according to the investigator rendered the patient inappropriate for the study, abnormal preoperative laboratory values (aspartate aminotransferase >2.5×upper limit of normal, alanine aminotransferase >2.5×upper limit of normal, bilirubin >1.5×upper limit of normal, or creatinine >1.5×upper limit of normal), or need for opioid antagonists or benzodiazepine antagonists. Medications known to induce CYP3A4, such as phenytoin, carbamazepine, barbiturates, rifampicin, or rifabutin, were prohibited within 30 days of the study start; those known to be CYP3A4 substrates (terfenadine, pimozide, cisapride, or astemizole) or CYP3A4 inhibitors (clarithromycin, ketoconazole, or itraconazole) were prohibited within 7 days of the study start.

The gender-stratified randomization schedule was computer-generated by the sponsor. In order to ensure in-house blinding, the schedule was created by an assistant statistician who was otherwise not involved with the study. On the day of surgery, patients were randomized to receive one of three antiemetic treatments before operation: oral aprepitant 40 mg, oral aprepitant 125 mg, or i.v. ondansetron 4 mg. Patient and investigator blinding was maintained with matching placebos. The sponsor provided supplies of aprepitant, placebo matching aprepitant, and blinded allocation schedules. Each site designated an unblinded pharmacist otherwise not involved with the study to receive, store, and prepare the ondansetron and saline placebo.

Aprepitant or placebo was given within 3 h of anticipated induction of anaesthesia, and i.v. ondansetron or placebo was infused over 2–5 min immediately before induction, as indicated in the approved prescribing information for ondansetron.[19]

The anaesthesia regimen consisted of optional premedication with a benzodiazepine; induction with any anaesthetic agent; neuromuscular blocking agents; opioids; maintenance of anaesthesia with nitrous oxide (50–70%) with a volatile anaesthetic; and neostigmine (2–5 mg) as needed. Additional prophylactic antiemetics were prohibited within 24 h before or after surgery except for postoperative rescue therapy, which was offered if the patient requested it, had nausea lasting longer than 15 min, or had >1 episode of vomiting/retching. The type of rescue therapy was chosen by the investigator.

The duration of anaesthesia and all medications given intraoperatively were recorded. From 0 to 48 h after placement of the last suture/staple, all emetic episodes (oral expulsion of stomach contents or non-productive retches) or use of rescue therapy were recorded. Using an 11-point verbal rating score (VRS), patients rated nausea from 0 ('no nausea') to 10 ('nausea as bad as it could be') at 2, 6, 24, and 48 h after operation, at any time the patient complained of nausea, and just before receiving rescue medication.

Tolerability was evaluated by physical examinations, laboratory tests, and reporting of adverse events (AEs). Twelve-lead electrocardiograms were obtained at baseline and 24 h after surgery, with particular attention paid to QTc intervals. Awakening time (interval between end of surgery and the patient's ability to obey commands) and duration of recovery from anaesthesia (interval between end of surgery and achievement of Aldrete postanaesthesia recovery score of 8 on a 0–10 scale[20]) were also recorded. Patients were discharged $\geq$24 h after operation and if discharged before 48 h were contacted at that timepoint by the study coordinator to record emetic episodes, use of rescue, and nausea VRS assessment. A follow-up visit or telephone call to the clinic was required within 3 weeks of surgery, at which time any AEs occurring within 14 days after surgery were documented.

Statistical analysis

The sponsor managed the data and performed the analyses for this study. The primary endpoints for the efficacy analysis were: (1) complete response (no vomiting and no use of rescue therapy) over 0–24 h after surgery, to be analysed first for non-inferiority of aprepitant, followed by superiority of aprepitant if non-inferiority was demonstrated, and (2) no vomiting over 0–24 h after surgery, to be tested for superiority of aprepitant. Clinical trials are commonly conducted to show non-inferiority of an experimental treatment against an active control. While equivalence trials have the objective of showing similar effects between the treatments investigated, non-inferiority trials have the objective of showing that an experimental treatment has an effect that is better than or not worse than the active control effect. Therapeutic non-inferiority is typically defined in terms of a fixed margin, δ. Non-inferiority is declared when there is a high degree of confidence (based on a 95% CI) that the effect of the control is not greater than that of the treatment by more than δ. The study was originally designed to test the single hypothesis of superiority of aprepitant for complete response but, while the study was ongoing, results were obtained from the first trial, which prompted reconsideration of the importance of the no vomiting endpoint. An adjustment was therefore made such that superiority of aprepitant for no vomiting and non-inferiority for complete response were assessed as dual primary hypotheses, with sample size increased accordingly to maintain statistical power. These modifications, which were made before completion of enrolment, treatment, and unblinding of the database, did not affect the study design or consent form. The changes were implemented in adherence with standard regulatory guidelines[21] and with US and European Union regulatory consent; approval of aprepitant for the PONV indication included the findings of this study.[17 22]

The secondary efficacy endpoint of this study was no vomiting in the first 48 h after surgery. Exploratory endpoints included no use of rescue in the first 24 h after surgery, peak nausea score (indicating the patient's worst nausea) on the VRS in the first 24 h, and time to first vomiting in the first 48 h.

The therapeutic non-inferiority fixed margin (δ) was calculated as one-half the smallest reported relative effect of ondansetron to placebo (10 percentage points), based on review of placebo-controlled studies showing that prophylaxis with ondansetron is associated with approximately a 20–30% reduction in the incidence of PONV when compared with placebo.[23] Because the present trial used a logistical regression analysis for which the natural metric is the odds ratio, the non-inferiority margin of 0.65 was calculated on the odds ratio scale, corresponding to the 10 percentage-point difference on the raw percentage scale. Thus, non-inferiority was formally defined as a lower bound $>$0.65, and superiority as a lower bound $>$1, for the 1-sided 95% CI for the odds ratio of aprepitant *vs* ondansetron. An additional analysis using a more conservative 2-sided CI was also performed using the same definitions for non-inferiority and superiority.

The primary efficacy analyses were performed on a modified intent-to-treat population, which included all patients who received the study drug, underwent protocol-defined surgery, and had at least one post-treatment efficacy assessment. Treatment comparisons for the efficacy endpoints were made using logistical regression models including terms for treatment and investigative sites. Interactions between treatment and investigative sites were tested at a 10% significance level, and all tests of hypotheses used a 2-sided significance level of 5% unless stated otherwise. A step-down procedure was used to account for multiple tests for the two primary hypotheses and also within the primary hypotheses (two doses of aprepitant compared with ondansetron) as follows: aprepitant 125 mg and ondansetron were compared at the 0.05 significance level; if the difference in complete response rate was significant, aprepitant 40 mg was then compared with ondansetron at the 0.05 level. The two aprepitant doses were not formally statistically compared with each other in this study.

The single highest nausea VRS score was calculated for each patient over 0–24 h as the individual peak nausea score; treatment groups were compared using Wilcoxon rank-sum test. On the basis of the recent research on nausea categorization scales suggesting that a VRS score

of 4 is a relevant cutoff representing mild (i.e. not significant) nausea,[24] a *post hoc* analysis was conducted comparing percentages of patients in each treatment group with peak scores in the range of 0 (i.e. no nausea) to 4 (no significant nausea). Kaplan–Meier curves were generated for the time to first emesis during the first 48 h and log-rank testing was used to compare treatments. The rates of incidence of emetic episodes were also compared between groups using a Poisson regression analysis, which took into account the use of rescue medication.

The study was powered to achieve a minimum of 80% on both primary hypotheses. Assuming a 1-sided significance level of 0.05, a complete response rate of 45% for ondansetron, and the prespecified non-inferiority margin of 0.65 for the odds ratio of aprepitant 125 mg *vs* ondansetron, the study had 80% power to declare aprepitant 125 mg to be non-inferior to ondansetron in terms of complete response in the 0–24-h interval. For the no vomiting endpoint (0–24 h), based on a sample size of 280 evaluable patients per treatment group and assuming a 2-sided significance level of 0.05 for superiority testing, the study had 99% power to detect a 15 percentage-point difference between aprepitant 125 mg and ondansetron (e.g. 90 *vs* 75%).

The primary safety hypothesis was that aprepitant 40 and 125 mg would be well tolerated. The tolerability analyses and displays included all patients who received study drug. Pairwise treatment comparisons were made using Fisher's exact test. Tests of significance were performed and the corresponding risk differences and 95% CI calculated using the method of Miettinen and Nurminen;[25] no multiplicity adjustment was used. Relatedness of any AE to study drug was determined by the investigator. In addition, to detect possible drug interactions, serious AEs of excessive sedation and respiratory depression were adjudicated in blinded fashion by two physicians not involved with the study.

Results

Study population

Figure 1 shows patient accounting. Among 1004 patients screened, a total of 922 patients were randomized. Of these, 30 patients were excluded from the tolerability and efficacy analyses because they either did not receive any study drug (n=25) or received partial study drug that was found after unblinding to have been the inactive (placebo) portion of the regimen (n=5). In addition to these 30 patients, 26 other patients were excluded from the efficacy analyses for various reasons as shown in the figure. Reasons for discontinuation were similar among treatment groups, with a clinical AE (one patient in the aprepitant 40 mg group, three patients in the aprepitant 125 mg group, and two patients in the ondansetron group), loss to follow-up (0, 1, and 1 patient in the three respective groups), and withdrawal of consent (1, 1, and 2 patients in the respective groups) reported most commonly; other reasons included change in surgical/anaesthetic plan or patient loss of eligibility.

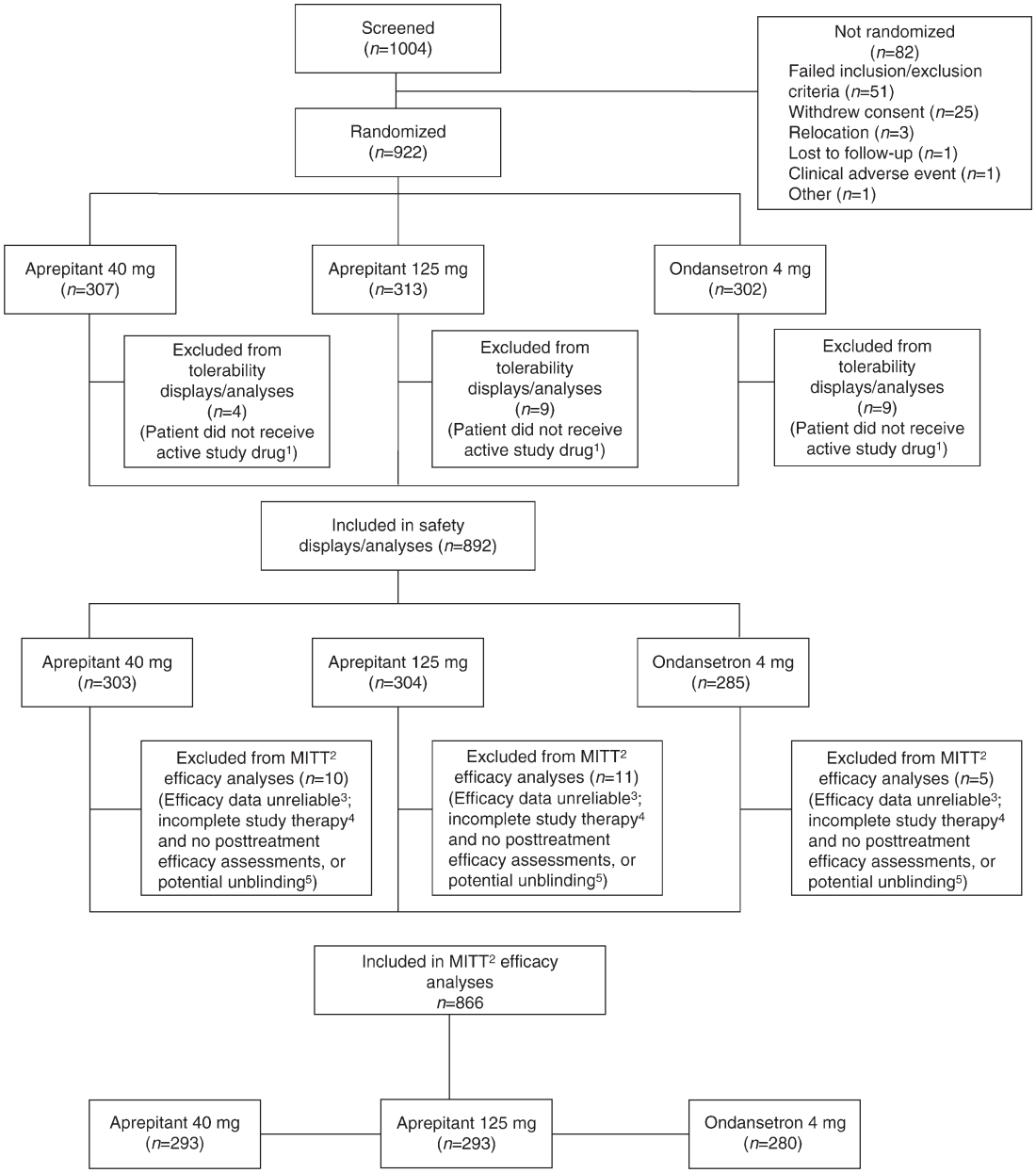
As shown in Table 1, the treatment groups were similar in terms of patient characteristics and other baseline characteristics including types of surgery, secondary diagnoses, types of rescue therapy used in the first 24 h after surgery, and risk factors for PONV. Among patients (<10%) who did not undergo open abdominal gynaecological surgery, procedures included cholecystectomy, hernia repair, intestinal resection, and prostatectomy. No significant interactions (P>0.1) were observed between treatment and investigative site, age, duration of surgery, or risk factors for PONV (smoking status, history of PONV, or history of motion sickness). Although randomization was stratified by gender, gender was not included in the model because <10% of patients were male.

Efficacy

Complete response was achieved in 64% of patients in the aprepitant 40 mg group (odds ratio of aprepitant to ondansetron=1.4, lower bound of the 1-sided 95% CI=1.08), 63% in the aprepitant 125 mg group (odds ratio=1.4, lower bound of the 1-sided 95% CI=1.04), and 55% in the ondansetron group (Fig. 2). For both doses of aprepitant, the lower bound of the 1-sided 95% CI for the odds ratio was >0.65, indicating non-inferiority according to the prespecified criteria. The additional analysis using a more restrictive 2-sided CI confirmed the non-inferiority of both doses of aprepitant when compared with ondansetron 4 mg (lower bound of 95% CI: aprepitant 40 mg *vs* ondansetron=1.02; aprepitant 125 mg *vs* ondansetron= 0.99). The lower bound of the 95% CI for the odds ratio of aprepitant 125 mg *vs* ondansetron was <1 and thus did not meet the superiority criterion. Therefore, according to the step-down procedure, further testing was stopped for the complete response endpoint.

The percentage of patients with no vomiting over 0–24 h was significantly higher in both the aprepitant 40 mg (84%) and the aprepitant 125 mg group (86%) than in the ondansetron group (71%); the odds ratios were 2.1 for aprepitant 40 mg *vs* ondansetron and 2.5 for aprepitant 125 mg *vs* ondansetron (P<0.001 for both ratios) (Fig. 3).

As shown in Figure 3, both aprepitant groups were also superior to ondansetron for the secondary endpoint of no vomiting over 0–48 h (82% for aprepitant 40 mg, 85% for aprepitant 125 mg, and 66% for ondansetron; P<0.001). Odd ratios for the 0–48 h comparisons were 2.1 (aprepitant 40 mg *vs* ondansetron) and 2.8 (aprepitant 125 mg *vs* ondansetron) (P<0.001 for both ratios). Kaplan–Meier curves showed that compared with ondansetron, aprepitant delayed the time to first vomiting episode (P<0.001 based on the log-rank test) (Fig. 4).



[1]Because of incorrect preparation or administration of study drug at the site, patient either received no study drug or received partial study drug found to be inactive (placebo) after unblinding
[2]Modified intent-to-treat
[3]Unreliable efficacy data=18 patients from a total of two sites had inadequate source documentation, unreliable information supporting primary efficacy parameters such as nausea, rescue, and 24 h postoperative monitoring, or protocol/GCP violation, as determined by Sponsor auditing of study site. Data from these patients were included in the tolerability assessments
[4]Patient received the blinded oral capsule (aprepitant or placebo in a bottle), but did not receive the blinded i.v. solution (ondansetron or placebo in a vial). These patients were not included in the efficacy analyses. However, regardless of whether surgery was performed, patients who received aprepitant in the bottle were included in the safety analyses; patients who received only oral placebo were not
[5]One patient in the entire study was reported to have been potentially unblinded by study site personnel; data were included in tolerability assessments

Fig 1 Study flow chart.

The treatment groups were similar in terms of no use of rescue therapy in the 0–24-h time interval (Table 2). In the Poisson regression analysis, in which rates of incidence of vomiting were adjusted for use of rescue therapy, the ratio of episodes of vomiting was 1:2 for aprepitant 40 mg *vs* ondansetron and 1:2 for aprepitant 125 mg *vs* ondansetron. Because it has been reported in the literature that a second (i.e. rescue) dose of ondansetron may not be

Table 1 Baseline characteristics by treatment group for all patients who received active study drug, and types of rescue therapy in the modified intent-to-treat population. No differences were observed across study groups. [#]For aprepitant 40 mg, *n*=292; for aprepitant 125 mg, *n*=293; for ondansetron, *n*=279. [$]In modified intent-to-treat population; for aprepitant 40 mg, *n*=293; for aprepitant 125 mg, *n*=293; for ondansetron, *n*=280. [†]Non-smoker; female; history of PONV and/or motion sickness; use of posoperative opioids. [‡]P1=normal healthy person; P2=patient with mild systemic disease; P3=patient with severe disease

	Aprepitant 40 mg (*n*=303)	Aprepitant 125 mg (*n*=304)	Ondansetron 4 mg (*n*=285)
Age (yr)			
Mean (SD)	46 (11)	46 (11)	45 (11)
Range	19–84	18–84	21–84
Race (%)			
Black	11	13	9
White	48	47	51
Hispanic American	17	16	17
Asian	10	10	11
Other	14	14	12
Type of surgery (%)			
Gynaecological	81	81	83
Non-gynaecological	19	19	17
Duration of anaesthesia, h (mean; SD)[#]	2.0 (1.0)	1.9 (1.0)	1.8 (0.9)
Nitrous oxide (% of patients[$])	100	100	99
Midazolam (% of patients[$])	57	55	56
Neostigmine (% of patients[$])	85	84	83
Postoperative opioids (0–24 h) (% of patients[$])	95	95	97
History of PONV (%)	17	13	18
History of motion sickness (%)	14	15	14
Tobacco use (%)			
Never	70	68	69
Ex-user	15	13	11
Current	15	19	19
Female (%)	90	90	93
Number of risk factors for PONV[†] (%)			
0	0.3	0.3	0.4
1	5	6	5
2	26	27	23
3	50	53	54
4	18	14	19
ASA status[‡] (%)			
P1	56	54	53
P2	41	43	43
P3	2	3	4
Type of rescue therapy (0–24 h) (%)			
Dolasetron	2	1	2
Granisetron	1	1	1
Ondansetron	15	16	13
Dexamethasone	3	4	3
Betamethasone	0.3	0	0
Droperidol	2	3	3
Haloperidol	2	0.3	1
Lorazepam	0	0.3	0
Midazolam	0	0	1
Cyclizine	0.3	1	0
Dimenhydrinate	3	3	4
Metoclopramide	14	14	18
Prochlorperazine	0.3	2	0.4
Promethazine	3	4	6
Scopolamine	0.3	0.3	0

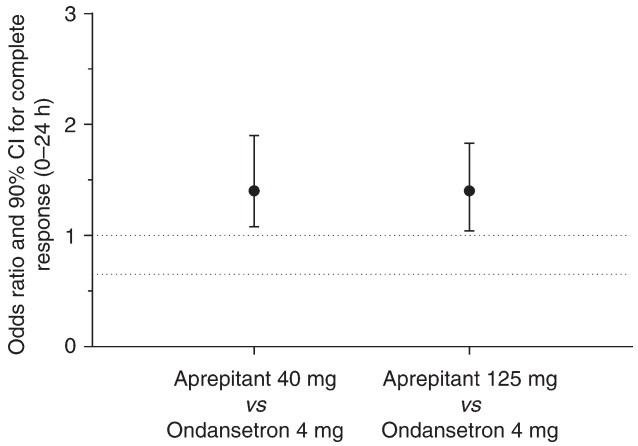


Fig 2 Odds ratios with 90% CI for aprepitant *vs* ondansetron for complete response in the first 24 h after surgery, by treatment group (modified intent-to-treat population). Two-sided 90% CI are shown for display purposes; the analysis was based on 1-sided 95% lower bound CI, which correspond to the 2-sided lower 90% CI shown in the figure (i.e. the lower error bar on each plot can be read as either a 1-sided 95% CI or a 2-sided 90% CI). Non-inferiority of aprepitant when compared with ondansetron was defined by a lower bound >0.65 for the CI of the odds ratio. Superiority of aprepitant when compared with ondansetron was indicated by a lower bound >1.0 for the CI of the odds ratio. $P<0.1$ for both odds ratios.

effective in patients who have already received ondansetron as prophylaxis,[26] a subanalysis was performed to examine the effect of ondansetron as rescue after ondansetron as prophylaxis. Among patients in the ondansetron group who took any rescue therapy, the no-vomiting rates were not significantly different among those rescued with

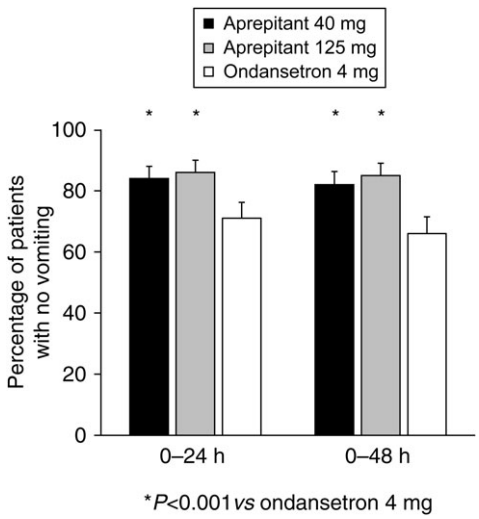


Fig 3 Proportions of patients with no vomiting 0–24 and 0–48 h after surgery, by treatment group (modified intent-to-treat population). For each group, the error bar represents the value of the upper bound of the 95% CI for the percentage of patients achieving the endpoint. For 0–24 h, *n*=293 for aprepitant 40 mg, *n*=293 for aprepitant 125 mg, and *n*=280 for ondansetron 4 mg. For 0–48 h, *n*=292 for aprepitant 40 mg, *n*=290 for aprepitant 125 mg, and *n*=279 for ondansetron 4 mg.

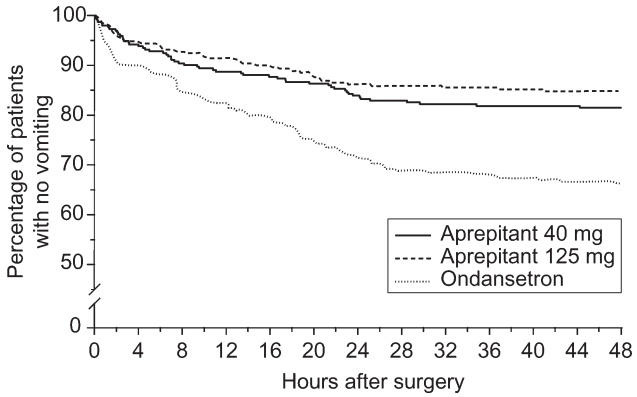


Fig 4 Kaplan–Meier curves for the time to first vomiting during the 48 h after surgery.

ondansetron (no vomiting=74%), those rescued with other medications (no vomiting=77%), and those who used any type of rescue (ondansetron or other medication) (no vomiting=76%).

The distribution of peak nausea scores was lower in both aprepitant groups *vs* ondansetron ($P<0.05$ for both comparisons) (Table 2). More patients in the aprepitant groups had no significant nausea (VRS≥4), when compared with the ondansetron group; the odds ratios, favouring aprepitant, were 1.4 (95% CI: 1.0–2.0) for aprepitant 40 mg and 1.3 (95% CI: 1.0–1.9) for aprepitant 125 mg. Also, in patients who did not need rescue in the first 24 h, the peak nausea score was lower in the aprepitant 40 mg group when compared with ondansetron, with about 68% of these patients reporting a peak nausea score of 0 in the aprepitant 40 mg group *vs* about 60% of patients in the ondansetron group.

Tolerability

A summary of AEs is displayed in Table 3. There were no significant between-treatment differences in the incidence of AEs. Four patients (three in the aprepitant 40 mg group and one in the aprepitant 125 mg group) had a serious AE consistent with respiratory depression or excessive sedation, but none of these was considered related to study drug. One serious laboratory AE (increased liver transaminase levels) was reported for a patient in the ondansetron group. The most commonly reported AEs (>5%) were pyrexia, constipation, headache, and bradycardia (Table 3); rates were similar across groups. The treatment groups did not differ in terms of awakening time, duration of recovery from anaesthesia, or percentages of patients with QTc interval prolongations at 24 h after surgery (QTc interval data shown in Table 3).

Table 2 No use of rescue therapy and peak nausea scores, by treatment group. [$]VRS=11-point verbal rating scale (0=no nausea, and 10=nausea as bad as it could be); analysis based on distribution of peak scores. *$P<0.05$ for aprepitant *vs* ondansetron

	Aprepitant 40 mg ($n=293$)	Aprepitant 125 mg ($n=293$)	Ondansetron 4 mg ($n=280$)
No use of rescue therapy (0–24 h) (%)	67	65	63
Peak nausea VRS score[$] (0–24 h)			
Median (interquartile range)	2 (0–6)*	2 (0–7)*	4 (0–8)
No significant nausea (peak VRS score 0–4) (%)	62*	60	53

Discussion

The present study was the second of two trials characterizing the efficacy and tolerability of the NK_1 antagonist

Table 3 Summary of AEs. All patients who took study drug were included in the tolerability analyses and displays. [#]No statistically significant between-treatment differences were observed ($P>0.05$ for aprepitant *vs* ondansetron). [$]AEs considered by the investigator to be possibly, probably, or definitely related to study drug. [##]Nausea and vomiting were considered AEs if they occurred after the first 48 h after surgery, or at any time if determined by the investigator to be serious, drug-related, or result in discontinuation. [†]Among all patients with test result reported postbaseline [(aprepitant 40 mg ($n=302$); aprepitant 125 mg ($n=299$); ondansetron 4 mg ($n=284$)]. No statistically significant differences were seen between the aprepitant groups and the ondansetron group, for the AEs shown. [‡]Among randomized patients who took at least one dose of active study medication and had at least one postbaseline QTc measurement ($n=288$, 284, and 275 for the respective groups)

Percentage of patients	Aprepitant 40 mg ($n=303$)	Aprepitant 125 mg ($n=304$)	Ondansetron 4 mg ($n=285$)
With ≥1 clinical AE[#]	52	59	54
With drug-related[$] clinical AEs[#]	4	7	6
With serious clinical AEs[#]	9	10	11
Discontinued because of a clinical AE[#]	0.3	0.7	0.4
With most common clinical AEs (≥5% in any treatment group[#])			
Bradycardia	5	6	4
Constipation	7	4	6
Nausea[##]	4	5	3
Pyrexia	7	7	11
Headache	4	7	5
With ≥1 laboratory AE[# †]	14	16	15
With most common laboratory AEs (in >2% in any treatment group[†])			
Decreased haemoglobin	5	7	6
Increased alanine aminotransferase	2	2	3
Increased aspartate aminotransferase	2	2	3
Decreased albumin	3	2	2
Decreased potassium	3	2	1
Red blood cells urine positive	0.7	2	0.7
With QTc interval prolongation at 24 h (%)[‡]			
<30 ms	43.4	48.2	40.0
30–60 ms	9.4	9.2	11.6
>60 ms	1.0	0.4	3.3

aprepitant, when orally administered, in a large surgical population who received volatile anaesthetics. For clarity in distinguishing effects of aprepitant *vs* ondansetron without the potential confounding influence of other prophylactic antiemetics, the study was designed as a comparison of monotherapies. As was observed in the previous study,[18] aprepitant provided protection similar to that of ondansetron on the complete response endpoint (no vomiting and no use of rescue therapy over 0–24 h). Also, both doses of aprepitant were significantly better than ondansetron for the prevention of vomiting over 0–24 h. The improved antiemetic efficacy of aprepitant was maintained over 0–48 h, consistent with the short half-life of ondansetron and the longer duration of action of aprepitant (half-life 9–13 h).[17 19] Patients taking aprepitant were more than twice as likely to be protected from vomiting when compared with patients taking ondansetron, and aprepitant delayed the time to first vomiting compared with ondansetron. The superiority of aprepitant on the no vomiting endpoint was still apparent in an analysis, which adjusted for use of rescue therapy. Although no formal statistical comparisons between the two aprepitant doses were performed, they appeared to have similar efficacy, suggesting a plateau in response.

Two other aspects of the study results that were of interest concerned: (1) the possible lack of effectiveness of ondansetron as rescue for patients whose initial antiemetic was ondansetron,[26] and (2) the timing of administration of prophylactic ondansetron. A subanalysis performed to assess the first of these considerations showed that in this study, vomiting in the ondanestron group was not significantly affected by the type of rescue therapy given (ondansetron *vs* any other medication including droperidol or dexamethasone). With regard to the second consideration, some small studies have shown that timing of the initial prophylactic dose of ondansetron (i.e. giving ondansetron at the end of surgery rather than before induction) may increase its antiemetic efficacy.[27] Because the design of the present study required that prophylactic ondansetron be given before induction according to the product label, it cannot be determined what effect, if any, the timing of administration may have had on the efficacy of ondansetron.

As a more subjective endpoint, nausea can be more difficult to measure than vomiting.[28] Based on the VRS used in this population, aprepitant had better antinausea efficacy than ondansetron, as reflected by the significantly lower distribution of VRS scores with aprepitant. The profiles of VRS scores among groups also supported enhanced antinausea efficacy with aprepitant: more patients taking aprepitant had no nausea or no significant nausea, and the most severe level of nausea was reported more often in patients taking ondansetron. While rescue can influence vomiting, nausea can influence the use of rescue, and is subject to interpatient differences both in the experience of nausea itself, and in the threshold at which a patient requests rescue. The intricacies of these relationships pose particular challenges for assessment of total control of PONV.

In general, the incidence and profile of clinical and laboratory AEs, of which pyrexia, constipation, headache, and decreased haemoglobin were most common, were typical of a population of surgical patients and were comparable across groups. As aprepitant has an inhibitory effect on CYP3A4, it was anticipated that awakening time and/or duration of recovery from anaesthesia would be prolonged if aprepitant had a clinically significant interaction with midazolam or fentanyl, both of which are CYP3A4 substrates. However, awakening time and duration of recovery did not differ between the aprepitant and the active control, and there were no study-drug-related AEs consistent with respiratory depression or excessive sedation. On the basis of these results, ondansetron and aprepitant, a dose-dependent inhibitor of CYP3A4,[17] did not appear to differ in terms of potential for interaction with CYP3A4-metabolized drugs commonly given to surgical patients, such as midazolam or fentanyl. Similarly, based on visual inspection of data for use of analgesics including opioid(s) across groups, there was no observable indication of a difference between treatments in terms of influence on mechanism(s) of pain.

In this study, the incidence of PONV in untreated patients is not known, but given the previously documented efficacy of aprepitant in the postoperative setting, and the fact that placebo-controlled trials may be unethical if patients in a high-risk population are assigned to receive placebo instead of an effective therapy, the use of a placebo group was not appropriate. Thus, the study demonstrated the improvements in protection against vomiting and nausea afforded by aprepitant when tested against a $5HT_3$ RA with previously established efficacy in this setting. Aside from enhanced patient comfort and the potential for earlier discharge from the recovery room,[29 30] the clinical benefits of improved antiemetic protection are particularly relevant in settings where postoperative vomiting may lead to clinical complications, especially among patients who undergo specific surgeries such as retinal, oesophageal, or maxillary surgeries, or those who require jaw-wiring.[29 31–37] Because the efficacy profile of aprepitant 40 mg was not clinically different from that of 125 mg, the 40 mg dose appeared to be adequate to provide improved PONV prophylaxis. Doses $<$40 mg have not been studied. Further study is needed to characterize the clinical profile of aprepitant in other settings such as primary prevention of PONV in children, treatment of established nausea and vomiting in surgical patients, and efficacy with non-volatile anaesthetic regimens, and its potential usefulness in combination with other antiemetics as a part of a multimodal prophylactic regimen.

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