

# Phase II Study to Evaluate the Safety and Efficacy of the Oral Neurokinin-1 Receptor Antagonist Casopitant (GW679769) Administered with Ondansetron for the Prevention of Postoperative and Postdischarge Nausea and Vomiting in High-risk Patients

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## ABSTRACT

**Background:** In recent years, there has been an increased interest in using a multimodal approach with combined agents to treat postoperative nausea and vomiting. This study evaluated whether the addition of an oral dose of the neurokinin-1 receptor antagonist casopitant improved the antiemetic efficacy of an intravenous dose of ondansetron hydrochloride.

**Methods:** The authors enrolled 702 premenopausal or perimenopausal, nonsmoking, female patients aged 18–55 yr with a history of postoperative nausea and vomiting and/or motion sickness undergoing a laparoscopic or laparotomic

gynecologic surgical procedure or laparoscopic cholecystectomy with general anesthesia. Subjects were randomized to one of five treatment arms: standard ondansetron 4 mg with casopitant at 0, 50, 100, or 150 mg, or 0 mg ondansetron with casopitant at 150 mg (the latter arm was considered an exploratory study group and was included in the safety analysis but not in the efficacy analysis).

**Results:** A significantly greater proportion of patients in all of the active casopitant plus ondansetron groups achieved a complete response (*i.e.*, no vomiting, retching, rescue medication, or premature withdrawal) during the first 24 h postoperatively *versus* those in the ondansetron-alone group (59–62% *vs.* 40%, respectively;  $P = 0.0006$ ). All active doses seemed to be well tolerated; headache, dizziness, and constipation were the most frequently reported adverse events.

**Conclusions:** Compared with ondansetron alone, the casopitant and ondansetron combination results in superior emesis prevention during the first 24 h postoperatively in female patients with known risk factors for postoperative nausea and vomiting.

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### What We Already Know about This Topic

- ❖ Combination drug therapy can further reduce postoperative nausea and vomiting compared with single-agent treatment

### What This Article Tells Us That Is New

- ❖ Combining ondansetron with a neurokinin-1 receptor antagonist (casopitant) increased the proportion of patients with no vomiting, retching, rescue medication, or premature withdrawal than ondansetron alone

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

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POSTOPERATIVE nausea and vomiting (PONV) remains the most frequently reported patient complaint after anesthesia,<sup>1,2</sup> and for patients, it is a greater concern than postoperative pain.<sup>3</sup> PONV occurs in approximately 20–30% of patients undergoing surgical procedures<sup>4,5</sup> and can lead to postsurgical complications such as fluid and electrolyte imbalances, surgical wound dehiscence, and aspiration of vomitus. PONV also delays discharge from the post-anesthesia care unit or requires an unanticipated admission to the hospital.<sup>6,7</sup> In patients undergoing laparoscopic cholecystectomy, the incidence of PONV ranges up to 72% in those who have not been given prophylactic treatment for preventing PONV.<sup>8,9</sup> Risk-stratification analyses<sup>10–12</sup> have identified four factors for predicting an increased risk for PONV: female sex, a history of motion sickness or PONV, nonsmoking status, and the use of postoperative opioids. Each of these is an independent risk factor, and the chance of experiencing PONV is proportional to the number of these risk factors. For these high-risk patients, PONV may occur in up to 70–80% of cases.<sup>11,13</sup>

Although considerable research has been performed in the treatment of PONV, there is still a need to improve on existing therapies. Monotherapy may reduce the incidence of PONV by only approximately 30%.<sup>14</sup> In recent years, there has been an increased interest in using a multimodal approach with combined agents to treat PONV because multiple receptors seem to be involved in the etiology of PONV.<sup>4</sup> One novel class of agents showing promise for the treatment of PONV are neurokinin (NK)-1 receptor antagonists, which may have utility in improving response rates over those achieved with existing PONV therapies.<sup>15,16</sup>

The oral NK-1 receptor antagonist casopitant (GW679769) has been shown to be active in the recognized ferret model of nausea and vomiting.<sup>17</sup> Therefore, we designed this phase II study (NKT102260) to evaluate the safety, efficacy, and pharmacokinetics of casopitant administered with intravenous ondansetron hydrochloride for the prevention of PONV in female patients undergoing surgical procedures associated with high emetogenic risk. The primary objective was to determine the optimal single dose of oral casopitant for the prevention of emesis during the first 24 h after emergence from anesthesia.

## Materials and Methods

### Patient Population

In this multicenter, randomized, double-blind, placebo-controlled, add-on dose-ranging phase II study, we enrolled premenopausal or perimenopausal, nonsmoking, female patients aged 18–55 yr with a history of PONV and/or motion sickness undergoing a laparoscopic or laparotomic gynecologic surgical procedure or laparoscopic cholecystectomy with general anesthesia. The institutional review board and ethics committee at each institution (University Health Network Research Ethics Board, Toronto, Ontario, Canada, and the Western Institutional Review Board, Olympia, Washington) approved the pro-

tol, and a written informed consent was obtained from the patients.

### Study Design

Patients were randomly assigned to one of five treatment arms. Four groups received 4 mg ondansetron with oral casopitant at 0, 50, 100, or 150 mg, and an additional exploratory study group received 0 mg ondansetron (intravenous placebo) with 150 mg casopitant. The exploratory study group was included in the safety analysis but not in the primary efficacy analysis. The results for the exploratory arm are presented in the interest of complete disclosure of study findings and should be interpreted accordingly. Investigational antiemetic drugs were administered before induction of anesthetics on the day of surgery. Casopitant (or a matching placebo in the ondansetron-alone group) was administered 60 min before induction of anesthesia. Ondansetron was administered intravenously (> 2–5 min) immediately before induction of anesthesia. The first dose of rescue antiemetic medication could be administered when medically indicated, if three emetic episodes occurred within a 15-min period, at physician discretion, or at any time on the subject's request.

All patients in the study were required to receive general endotracheal anesthesia. Induction was accomplished with propofol, and anesthesia was maintained with sevoflurane or desflurane. Nitrous oxide (maximum 30%) was allowed but not required. All patients were premedicated with midazolam or temazepam. Neuromuscular blockade was initiated and maintained with either depolarizing or nondepolarizing agents. Neostigmine (< 0.07 mg/kg) and glycopyrrolate (< 0.02 mg/kg) were used for reversal. Intraoperative analgesia was accomplished with fentanyl, remifentanyl, or morphine. Intraoperative ketorolac was allowed but not required 15–30 min before the end of surgery. Postoperatively, the analgesic regimen was left to the discretion of the investigator. Patient-controlled analgesia and analgesic adjuncts, such as nonsteroidal antiinflammatory drugs and pregabalin, were allowed.

The primary objective of our study was to determine the optimal dose of casopitant when administered in combination with intravenous ondansetron for the prevention of emesis (defined as vomiting or retching), by assessing the number of patients who achieved a complete response (defined as no vomiting, retching, rescue therapy, or premature withdrawal) during the first 24 h after the emergence from anesthesia.

Secondary efficacy endpoints included (1) the number of patients who achieved a complete response during each subsequent 24-h evaluation period (up to 120 h); (2) the extent of nausea experienced by patients during the 2-, 6-, and 24-h evaluation periods, as assessed by an 11-point, linear, numerical rating scale that was referred to as a Likert scale; (3) the extent of nausea experienced by patients daily at each subsequent 24-h evaluation period (up to 120 h), as assessed by a discrete Likert scale; (4) time to first emetic event; (5) time to rescue medication; (6) the number of patients who experienced vomiting during each 24-h evaluation period (up to 120 h); (7) the number of patients who experienced com-

plete protection (defined as complete response with maximum nausea < 3 on the Likert scale) during each 24-h evaluation period (up to 120 h); (8) the number of patients who experienced total control (defined as no vomiting, retching, rescue therapy, and premature withdrawal and a maximum nausea < 1 on the Likert scale) during each 24-h evaluation period (up to 120 h); (9) the safety of casopitant at various dose levels when administered in combination with intravenous ondansetron and with placebo; and (10) time to awakening and time to readiness for discharge. The pharmacokinetic and pharmacodynamic analyses have been presented elsewhere.<sup>18</sup>

### Evaluation of Study Endpoints

All statistical reporting was performed using SAS Version 9.1.3 (SAS Institute Inc., Cary, NC). The sample size for the study was calculated for a Cochran–Armitage linear trend test to detect a monotonic dose response, with a 2-sided type-1 error of 5%, 90% power, a 20% point difference between the lowest and highest doses, and an assumed 12% nonevaluable rate. The intent-to-treat statistical model was used to analyze response data. The intent-to-treat group included all patients who were randomized for treatment. Therefore, premature withdrawal from the study was considered treatment failure for the purposes of our analysis.

The exploratory 150 mg casopitant-alone treatment arm was not included in primary or secondary efficacy analyses. Efficacy information pertaining to emesis, assessments of nausea, and subject satisfaction was collected at least every 24 h until the end of the 120-h assessment period, using a subject diary. All patients were followed up for safety at least every 24 h until 120 h after emergence from anesthesia.

For the primary efficacy endpoint, the Cochran–Armitage trend test was performed to determine a monotonic dose increase from 0 to 150 mg (excluding the 150 mg-alone dose). To maintain the family-wise error rate at 0.05, the test was performed using the no statistical significance of trend procedure presented by Tukey *et al.*<sup>19</sup> Using the procedure, once the overall trend was determined to be statistically significant, ordinal contrasts were performed, deleting the highest dose, until the significance was no longer retained. The SAS MULTTEST procedure was used to fit the ordinal contrasts. In the event of a statistically significant result ( $P < 0.05$ ) being observed for the primary endpoint, our study was designed to further provide  $P$  values for each active dose compared with the placebo in all time periods for the following endpoints: complete protection, total control, vomiting, significant nausea (maximum scores  $\geq 3$  on the Likert scale), and nausea (maximum scores  $\geq 1$  on the Likert scale).

Time-to-event endpoints (time to first emetic event and time to first rescue medication) were summarized using Kaplan–Meier curves. Time-to-event data were summarized using quartiles (25th percentile, median, and 75th percentile) and the associated 95% CIs. Log-rank  $P$  values, which compare each treatment arm with placebo, were reported. If no event occurred at the end of the 120-h time period, the

observation was censored for the purpose of this analysis. Time to awakening and time to readiness for discharge were summarized descriptively using the mean and SD.

## Results

### Study Population

Fifty-three centers in six countries participated in this study; 702 patients were enrolled. As per the design, all patients were women, with a mean age of 38.9 yr (range, 18–56 yr). Demographic characteristics, including major risk factors for PONV, were well balanced among the treatment groups (table 1).

Approximately 90% of the patients completed the study (*i.e.*, completed all required assessments for the 24 h after the emergence from anesthesia on postoperative day 1) (table 2). The most frequent reasons for premature withdrawal were surgery being canceled or delayed, errors in randomization or dosing, and subject's decision to withdraw. Adverse events (AEs) leading to withdrawal from the study were reported in one subject in the 100 mg casopitant plus 4 mg ondansetron arm (amnesia) and two subjects in the 150-mg casopitant-alone arm (nerve compression and anaphylactic shock). None of these AEs was considered to be related to the study drug by the investigators.

### Efficacy

**Primary Endpoint.** A significantly greater proportion of subjects in all of the active casopitant plus 4 mg ondansetron treatment groups achieved a complete response during the 24-h assessment period (59–62%) compared with those in the ondansetron-alone group (40%; fig. 1). A monotonically increasing dose response was observed ( $P = 0.0006$ ); however, because each ordinal contrast was statistically significant, no minimally effective dose was established. All dose levels seemed to be effective. Thus, the lowest dose administered was effective with a significantly greater complete response rate compared with ondansetron alone (59.3 *vs.* 40.0%, respectively). In patients treated with casopitant alone (not included in the efficacy analysis), 71 of 142 patients (50%) achieved a complete response during the 24-h assessment period.

**Secondary Endpoints.** Compared with patients receiving 4 mg ondansetron alone, a significantly greater proportion of patients receiving casopitant plus ondansetron achieved a complete response during all assessment periods up to the 120-h postoperative time point. In general, the proportion of patients achieving a complete response during the 120-h postoperative period and the relative differences compared with ondansetron alone (36.4% for ondansetron alone) were similar to those observed for the first 24-h assessment period. In patients treated with casopitant alone, 62 of 142 patients (43.7%) achieved a complete response during all assessment periods up to the 120-h postoperative time point.

Significantly fewer patients in the casopitant plus ondansetron treatment groups experienced vomiting during the 24-h postoperative assessment period (4.3–9.3%) *versus* those in the ondansetron-alone group (28.6%; fig. 2). Simi-

**Table 1.** Demographic Characteristics of Study Participants

	0 mg CAS + 4 mg OND	50 mg CAS + 4 mg OND	100 mg CAS + 4 mg OND	150 mg CAS + 4 mg OND	150 mg CAS* + Placebo OND	Total
Variable	n = 140	n = 140	n = 140	n = 140	n = 142	N = 702
Age, yr	n = 130	n = 135	n = 134	n = 131	n = 132	N = 662
Mean	39.3	38.1	39.5	39.3	38.5	38.9
SD	8.15	8.24	8.58	7.84	8.33	8.23
Sex (women)	140 (100%)	140 (100%)	140 (100%)	140 (100%)	142 (100%)	702 (100%)
Race	n = 124	n = 121	n = 129	n = 124	n = 129	N = 627
African American/ African heritage, n (%)	13 (9)	17 (12)	17 (12)	17 (12)	21 (15)	85 (12)
American Indian or Alaska native, n (%)	0	2 (1)	3 (2)	2 (1)	2 (1)	9 (1)
Asian, n (%)	8 (6)	5 (4)	6 (4)	9 (6)	9 (6)	37 (5)
White, n (%)	103 (74)	97 (69)	103 (74)	96 (69)	97 (68)	496 (71)
Height, cm	n = 132	n = 135	n = 137	n = 132	n = 133	N = 669
Mean	164.0	162.7	162.9	163.2	163.4	163.3
SD	7.81	7.34	7.38	7.49	7.49	7.49
Weight, kg	n = 132	n = 135	n = 138	n = 132	n = 133	N = 670
Mean	75.1	75.1	73.8	74.6	74.5	74.6
SD	18.27	17.32	19.66	17.40	17.84	18.08
Risk factor	n = 140	n = 140	n = 140	n = 140	n = 142	N = 702
History of PONV, n (%)						
Yes	73 (52)	76 (54)	81 (58)	75 (54)	83 (58)	388 (55)
No	63 (45)	61 (44)	57 (41)	59 (42)	52 (37)	292 (42)
Missing	4 (3)	3 (2)	2 (1)	6 (4)	7 (5)	22 (3)
History of motion sickness, n (%)						
Yes	107 (76)	100 (71)	101 (72)	96 (69)	95 (67)	499 (71)
No	29 (21)	37 (26)	37 (26)	38 (27)	40 (28)	181 (26)
Missing	4 (3)	3 (2)	2 (1)	6 (4)	7 (5)	22 (3)
History of tobacco use, n (%)						
Yes	27 (19)	17 (12)	26 (19)	28 (20)	23 (16)	121 (17)
No	110 (79)	120 (86)	112 (80)	106 (76)	111 (78)	559 (80)
Missing	3 (2)	3 (2)	2 (1)	6 (4)	8 (6)	22 (3)
Parameter	n = 140	n = 140	n = 140	n = 140	n = 142	N = 702
Any surgical procedure, n (%)	130 (93)	135 (96)	132 (94)	130 (93)	131 (92)	658 (94)
Laparoscopic/laparotomic gynecologic procedure, n (%)	107 (76)	113 (81)	109 (78)	107 (76)	108 (76)	544 (77)
Laparoscopic cholecyst- ectomy, n (%)	23 (16)	21 (15)	23 (16)	22 (16)	23 (16)	112 (16)
Missing, n (%)	0	1 (< 1)	0	1 (< 1)	0	2 (< 1)
Duration of surgery, min	n = 129	n = 135	n = 131	n = 129	n = 130	—
Mean	77.2	77.0	80.5	77.8	79.1	—
SD	43.28	49.87	47.92	43.74	51.76	—

\* Exploratory arm, not included in primary efficacy analysis.

CAS = casopitant; OND = ondansetron; PONV = postoperative nausea and vomiting.

lar results were also observed during the entire 120-h postoperative assessment period; all three casopitant plus ondansetron treatment groups achieved a statistically significant reduction in the proportion of patients experiencing vomiting compared with the ondansetron-alone group. In patients treated with casopitant alone, 10 of 142 patients (7.0%) experienced vomiting during the 24-h assessment period, and 14 of 142 patients (9.9%) experienced vomiting during all assessment periods up to the 120-h postoperative time point.

There were no statistically significant differences in the proportion of patients who experienced nausea between the active casopitant treatment groups and the ondansetron-alone group during the 0- to 24-h assessment period or any of the subsequent assessment periods (fig. 3). However, nausea tended to be more severe in the ondansetron-alone group than in the groups receiving casopitant in combination with ondansetron in the 0- to 24-h assessment period, with a majority of patients in the former arm having a nausea severity of more than or equal to 6 (fig. 4).



**Table 2.** Reasons for Study Withdrawal

	0 mg CAS + 4 mg OND	50 mg CAS + 4 mg OND	100 mg CAS + 4 mg OND	150 mg CAS + 4 mg OND	150 mg CAS* + Placebo OND
Completion status	n = 140	n = 140	n = 140	n = 140	n = 142
Completed, n (%)	129 (92)	135 (96)	130 (93)	128 (91)	126 (89)
Prematurely withdrawn, n (%)	11 (8)	5 (4)	10 (7)	12 (9)	16 (11)
Primary reason for withdrawal, n (%)					
Adverse event	0	0	1 (< 1)	0	2 (1)
Protocol violation	0	0	2 (1)	0	2 (1)
Subject decided to withdraw	1 (< 1)	2 (1)	3 (2)	4 (3)	4 (3)
Sponsor terminated study	0	0	0	0	1 (< 1)†
Other	10 (7)	3 (2)	4 (3)	8 (6)	7 (5)

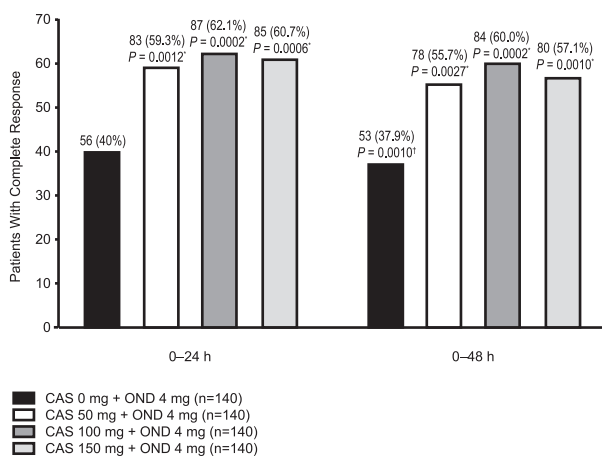
\* Exploratory arm, not included in primary efficacy analysis. † Sponsor terminated study because of completion of planned enrollment after patient had been screened.

CAS = casopitant; OND = ondansetron.

This discrepancy was not statistically significant and was not observed during the later intervals (24–48 h and 48–72 h), in which most patients had nausea at level 2 or lower irrespective of treatment arm. A total of 103 of 142 patients (72.5%) taking 150 mg casopitant alone experienced nausea in the 24-h assessment period (fig. 3); as with ondansetron alone, the majority of patients (58.5%) taking casopitant alone had a nausea severity of more than or equal to 6 (fig. 4) during the 24-h assessment period.

No statistically significant differences were noted between the treatment groups in the proportion of patients who achieved complete protection or total control during any assessment period. All three casopitant plus ondansetron treatment groups increased the time to the first emetic event and first rescue medication compared with the 4 mg ondansetron-alone group (figs. 5A and B). The mean and median times to awakening and readiness for discharge were similar across groups.

F5



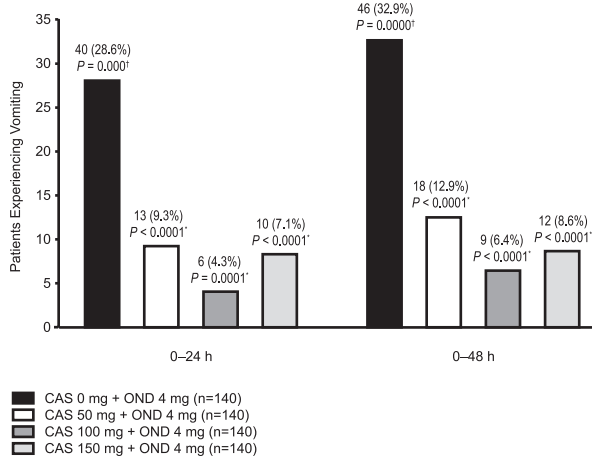
**Fig. 1.** Summary of complete response. Values shown represent n (%) achieving a complete response (no vomiting, retching, rescue medication, or premature withdrawal). \* Ordinal contrast P values: ordinal contrast tests if the highest dose, the next highest dose, and so on are different from ondansetron alone, in a hierarchical fashion. † P value determined using Cochran–Armitage trend test. CAS = casopitant; OND = ondansetron.

**Safety**

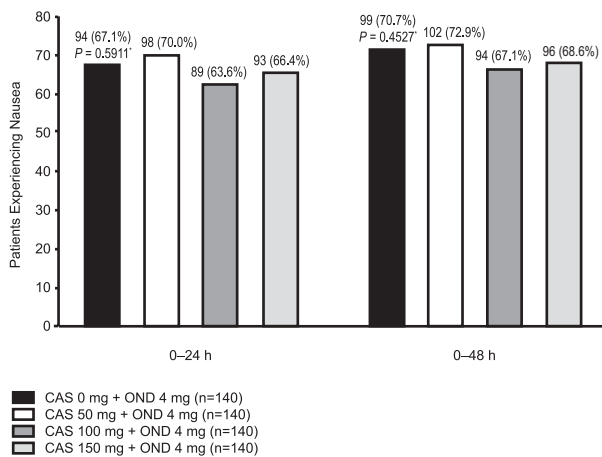
Approximately half the patients (52%) in the ondansetron-alone group and the active casopitant treatment groups (46–52%) experienced at least one AE (table 3). Headache was the only AE occurring in more than 10% of the patients in any treatment group and was the only severe AE reported in more than 1 patient in any treatment group. The majority of AEs were considered to be mild or moderate in intensity. No important differences were noted across the treatment groups, with the possible exception of abnormalities in liver function tests, which occurred in 6% of patients receiving 150 mg casopitant plus ondansetron but in only 2–3% of patients across the other four treatment groups (table 3).

T3

The incidence of drug-related AEs was comparable across the five treatment groups, ranging from 9% in the 100 mg casopitant plus ondansetron group to 18% in the 150 mg casopitant plus ondansetron group, and 15% in the ondansetron-alone and casopitant-alone groups. Headache was the most frequently reported drug-related AE, occurring in 9%



**Fig. 2.** Patients experiencing vomiting. \* Ordinal contrast P values: ordinal contrast tests if the highest dose, the next highest dose, and so on are different from ondansetron alone, in a hierarchical fashion. † P value determined using Cochran–Armitage trend test. CAS = casopitant; OND = ondansetron.



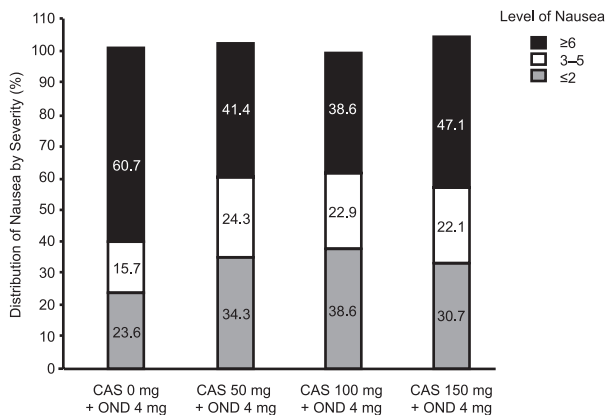
**Fig. 3.** Patients experiencing nausea. \* *P* value determined using Cochran–Armitage trend test. CAS = casopitant; OND = ondansetron.

of the patients in the 4 mg ondansetron-alone group and in 3–6% of the patients in the casopitant-treatment groups.

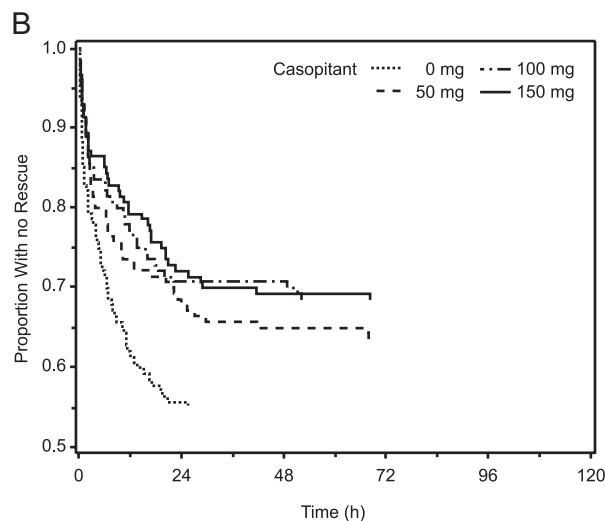
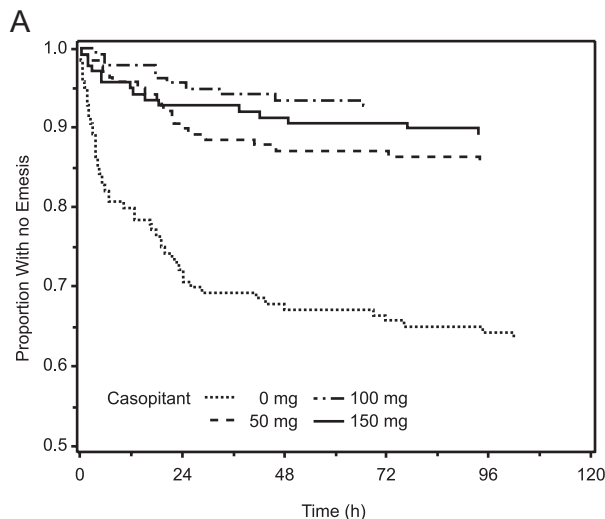
A total of 31 patients experienced at least one nonfatal serious AE (SAE) during the study. The proportion of patients with an SAE was similar across treatment groups. Of these SAEs, five reported by four patients were considered drug related: hemorrhage, dyspnea and pulmonary edema, hemorrhagic shock, and hyperglycemia. There were no fatal SAEs during the study.

**Discussion**

Because multiple receptors may be involved in the etiology of PONV,<sup>4</sup> prophylaxis against PONV, especially in high-risk populations, may be better achieved by using a combination of antiemetic agents that act on the different neurotransmitter receptors involved in the emetic pathway.<sup>20–22</sup> In our study, a significantly greater proportion of patients in all of the active casopitant plus ondansetron groups achieved a complete response of no vomiting, retching, rescue medication, or premature withdrawal during the first 24 h postoperatively compared with those in the ondansetron-alone group (59–62% vs. 40%).



**Fig. 4.** Proportion of patients by nausea level (0–24 h). CAS = casopitant; OND = ondansetron.



**Fig. 5.** Kaplan–Meier curves for time from emergence from anesthesia to (A) first emetic episode and (B) first rescue medication.

Casopitant is an NK-1 receptor antagonist developed for the prevention and treatment of PONV. The oral doses of casopitant used in the current study were based on unpublished NK-1 receptor occupancy data generated in a phase I positron emission tomography study in healthy subjects. An oral dose range of 50–150 mg was predicted to result in a 70 to more than 95% NK-1 receptor blockade in the striatal region of the brain at 24 h after a single dose of casopitant. Receptor occupancy in the striatal region is a surrogate for the nucleus tractus solitarius region of the brainstem—the presumed site of action—because the brainstem cannot be imaged quantitatively by positron emission tomography. Although the relationship between NK-1 receptor blockade in the striatum and prevention of PONV has not been established, studies with NK-1 receptor antagonists in the chemotherapy-induced vomiting setting suggest that a 24-h trough level of more than or equal to 95% NK-1 receptor blockade in the striatum is a reasonable surrogate for the prevention of nausea and vomiting *via* this centrally mediated mechanism.<sup>23</sup> These data have been correlated with clinical

**Table 3.** Adverse Events Reported by 3% or More of Patients in Any Treatment Group (Safety Population)

Adverse Event by Preferred Term	0 mg CAS + 4 mg OND (n = 130)	50 mg CAS + 4 mg OND (n = 135)	100 mg CAS + 4 mg OND (n = 134)	150 mg CAS + 4 mg OND (n = 131)	150 mg CAS + Placebo OND (n = 132)
Any adverse event	68 (52)	62 (46)	69 (51)	68 (52)	61 (46)
Headache	16 (12)	13 (10)	10 (7)	14 (11)	11 (8)
Dizziness	8 (6)	9 (7)	12 (9)	8 (6)	4 (3)
Constipation	13 (10)	4 (3)	12 (9)	6 (5)	8 (6)
Abdominal distension	3 (2)	4 (3)	0	3 (2)	6 (5)
Hyperglycemia	2 (2)	1 (< 1)	0	5 (4)	2 (2)
Hypotension*	4 (3)	4 (3)	5 (4)	4 (3)	4 (3)
Flatulence	7 (5)	0	5 (4)	1 (< 1)	3 (2)
Pruritus	8 (6)	4 (3)	4 (3)	4 (3)	4 (3)
Insomnia	4 (3)	2 (1)	2 (1)	3 (2)	5 (4)
Procedural hypotension*	2 (2)	3 (2)	1 (< 1)	3 (2)	6 (5)
Anemia	2 (2)	2 (1)	0	2 (2)	4 (3)
Chills	2 (2)	0	1 (< 1)	4 (3)	2 (2)
LFT abnormal†	4 (3)	4 (3)	3 (2)	8 (6)	3 (2)

Episodes of nausea or vomiting that occurred during the 120-h postoperative assessment period were reported as part of the efficacy assessment rather than as adverse events or serious adverse events, unless the severity was more than expected. Values are expressed as n (%).

\* The preferred term, "procedural hypotension," included the verbatim terms "intraoperative hypotension" and "postoperative hypotension." † At the time of the analysis, the Medical Dictionary for Regulatory Activities included the preferred terms "ALT increased," "AST increased," "hepatic enzyme increased," "blood bilirubin increased," and "liver function test abnormal." To enhance clarity, these five categories have been consolidated. Patients for whom more than 1 adverse event was reported (e.g., ALT increased and AST increased reported as separate events) are counted once.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAS = casopitant; LFT = liver function test; OND = ondansetron.

efficacy in randomized clinical trials for aprepitant,<sup>24,25</sup> the first NK-1 receptor antagonist approved for the prevention of chemotherapy-induced nausea and vomiting.

There are some limitations to the design of the current study, including the lack of a placebo arm in which no antiemetic medication was administered. Nausea and vomiting are highly likely to occur in patients with two or more risk factors, as in our population. Therefore, perioperative antiemetic prophylaxis is the standard of care in this population, and all subjects in the study did receive active preventative antiemetic care. In addition, although the baseline incidence of PONV is fairly well characterized based on type of surgery and other risk factors, we do not know the actual baseline incidence of PONV in our study population.

In our analysis, the primary endpoint of complete response was achieved in a significantly greater percentage of patients in all casopitant plus ondansetron treatment groups *versus* the ondansetron-alone (control) group during the first 24 h postoperatively ( $P = 0.0006$ ). Complete response was also achieved during the entire 120-h postsurgery period (54–57% in the casopitant plus ondansetron groups *vs.* 36% in the ondansetron-alone group;  $P = 0.0012$ ). A statistically significant advantage for casopitant plus ondansetron *versus* ondansetron alone was also observed for the outcomes of the proportion of patients who experienced vomiting, the time to first emetic event, and the time to first use of rescue medication. Furthermore, rescue use was higher in the ondansetron-alone group compared with the casopitant groups, implying that the benefits of casopitant in the post-24-h period may be higher than that suggested by these results.

There was no statistically significant difference between the treatment groups in the number and percentage of patients who experienced any nausea or significant nausea. However, a *post hoc* analysis of the severity of nausea over 72 h suggested that patients in the combination treatment groups tended to have mild or moderate nausea, whereas those in the ondansetron-alone group had a greater frequency of severe nausea.

It is important to note that, across all treatment arms, a paucity of events leading to treatment failure was observed after the first 24-h period. Because the incidence of PONV was low after 24 h, a positive treatment effect is difficult to detect.

Efficacy results were similar for all three doses of casopitant (in combination with ondansetron) analyzed in this study: 50, 100, or 150 mg. We were unable to establish a minimally effective dose of casopitant. In addition, a previously reported pharmacokinetic and pharmacodynamic evaluation showed that complete response rate did not differ with casopitant exposure (area under the concentration–time curve or concentration 24 h postdose) over the dose range of 50–150 mg.<sup>18</sup> Time-to-event analysis showed that the casopitant exposures produced by 50- to 150-mg doses provided adequate protection against emesis; however, when casopitant exposure from all subjects was ranked, subjects in the lowest quartile (25%) of exposure were at higher risk for requiring rescue medications.<sup>18</sup> These data suggest that casopitant doses less than 50 mg may not provide adequate protection against the need for rescue medication (*i.e.*, a complete response). All casopitant doses were active and well tolerated, and AEs were equally distributed across all treatment

groups. There were no deaths, and SAEs were reported with a similar spread of incidence across the four treatment groups.

In conclusion, a significantly greater proportion of patients in all of the active casopitant plus ondansetron groups achieved a complete response of no vomiting, retching, rescue medication, or premature withdrawal during the first 24 h postoperatively compared with those in the ondansetron-alone group (59–62% *vs.* 40%). Because the effect of all three doses of casopitant in combination with ondansetron was similar, in terms of both tolerability and efficacy, the most appropriate choice of dose of casopitant for future development in combination with ondansetron would be 50 mg. This dose represents the best choice in terms of minimizing patient exposure while retaining efficacy.

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