ORIGINAL ARTICLE

Casopitant and Ondansetron for Postoperative Nausea and Vomiting Prevention in Women at High Risk for Emesis

A Phase 3 Study

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Hypothesis: Postoperative nausea and vomiting (PONV) are associated with a variety of complications. Neurokinin subtype 1 receptor antagonists have antiemetic activity in the postoperative setting, and the neurokinin subtype 1 receptor antagonist casopitant mesylate (GW679769) was well tolerated and effective at reducing the incidence of PONV in phase 1 and phase 2 trials.

Design: A multicenter, randomized, double-blind, parallel-group, phase 3 analysis was designed to evaluate the safety and efficacy of casopitant in combination with a single intravenous dose of the serotonin subtype 3 receptor antagonist ondansetron hydrochloride for the prevention of PONV in the perioperative setting.

Setting: Forty-three centers in 11 countries.

Patients: We studied 484 women at high risk for developing PONV scheduled to undergo operations associated with high emetogenic risk.

Interventions: The women were randomized to receive a single dose of intravenous ondansetron, 4 mg, or oral casopitant, 50 mg, in combination with intravenous ondansetron, 4 mg.

Main Outcome Measures: The primary end point was the proportion of patients who achieved a complete response, defined as no vomiting, retching, or rescue therapy. Patients received a balanced anesthetic regimen.

Results: Between March 20 and August 31, 2006, 484 patients were enrolled in the study. Patients in the casopitant plus ondansetron group had a 68.7% rate of complete response during the first 24 hours after surgery compared with 58.7% in the ondansetron-only group ($P=.03$). The difference between groups in complete response from 24 to 48 hours (63.4% with ondansetron only vs 70.0% with ondansetron plus casopitant) was not significant. No vomiting for 0 to 24 hours was observed in 89.7% of the casopitant plus ondansetron group compared with 74.9% of the ondansetron-only group ($P<.001$). Oral casopitant administered in combination with ondansetron was well tolerated.

Conclusions: The results of this pivotal phase 3 study demonstrate that the combination of casopitant and ondansetron was superior to ondansetron only in patients at high risk for PONV.

Trial Registration: clinicaltrials.gov Identifier: NCT00326248

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Postoperative nausea and vomiting (PONV) can occur after local, regional, or general anesthesia and is associated with a variety of postsurgical complications that can adversely affect patient recovery and discharge.[1] Examples of common surgical procedures associated with increased risk of emesis include laparoscopic cholecystectomy and abdominal surgery for all patients, gynecologic procedures and breast surgery for women, and shoulder surgery for men. Volatile anesthetics have been reported to be associated with higher rates of PONV,[2] and intraoperative and postsurgical administration of opioids often leads to emesis.[3] Risk stratification analyses have identified female sex, a history of motion sickness or PONV, nonsmoking status, and the use of postoperative opioids as independent risk factors for PONV.[4,5] In higher-risk patients, PONV can occur at rates of 70% to 80%.[6,7] Because multiple receptors appear to be involved in the etiology of PONV, there is a growing consensus that 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.[8]

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Human studies have demonstrated that neurokinin subtype 1 receptor antagonists have antiemetic activity in the postoperative setting for prevention and treatment.[9,10] The neurokinin subtype 1 receptor antagonist aprepitant was found to be superior to the intravenous (IV) serotonin subtype 3 receptor antagonist ondansetron hydrochloride for the prevention of vomiting in the first 24 to 48 hours and comparable with ondansetron for nausea control, use of rescue therapy, and complete response.[11]

Casopitant mesylate (GW679769) is a potent and selective neurokinin subtype 1 receptor antagonist that is readily absorbed after oral administration with a mean absolute bioavailability of 57.0% and a median (range) time to maximal plasma concentration of 1.75 hours (1.0-4.0 hours). Casopitant is extensively metabolized, and nonclinical data suggest this occurs primarily via CYP3A4. The terminal plasma elimination half-lives of casopitant after single-dose administration of 150 mg of oral casopitant or 90 mg of IV casopitant were 17.0 and 15.6 hours, respectively. A major circulating metabolite, GSK525060 (M13), has a similar half-life.[12]

Casopitant has been investigated for the prevention and treatment of PONV and chemotherapy-induced nausea and vomiting. In previous phase 1 and 2 trials, casopitant at a 50-mg oral dose was well tolerated and reduced the incidence rate of PONV. In a repeat-dose pharmacokinetic interaction study[13] in healthy patients, no relevant effect on ondansetron kinetics was found after coadministration with single doses of casopitant, 30 and 90 mg.

On the basis of these results, this phase 3 study (NKT102553) was designed to evaluate the safety and efficacy of casopitant in combination with ondansetron for the prevention of PONV. The primary objective was to demonstrate the superiority of oral casopitant in combination with a single IV dose of ondansetron compared with a single IV dose of ondansetron only in the control of emesis during the first 24 hours after surgery in women who were predicted to have a high risk of emesis.

METHODS

PATIENT POPULATION

This multicenter, randomized, double-blind, parallel-group, phase 3 study (NCT00326248) enrolled only patients 18 years or older with American Society of Anesthesiologists Physical Status Classification of P1 or P2 (healthy or mild systemic disease, respectively) who had all 4 Apfel risk factors[4] for PONV (female sex, history of PONV and/or motion sickness, nonsmoker status, and anticipated to receive opioids postoperatively) and were scheduled to undergo 1 of the following surgical procedures: breast surgery, orthopedic shoulder surgery, or thyroid surgery and laparoscopic or laparotomic procedures for cholecystectomy, hysterectomy, or other gynecologic surgery.

All operations were anticipated to involve general anesthesia of at least 1 hour. Anesthetic regimens were not specified, but investigators were required to adhere to a balanced general anesthetic regimen as per their institutional guidelines and common practice. Propofol was permitted for induction of, but not maintenance of, anesthesia. Total IV anesthesia was not allowed in this study. Patients who were anticipated to require a nasogastric or oral-gastric tube with intermittent or continuous suctioning postoperatively were excluded from this study. Patients who had received medication with potential antiemetic activity in the 24-hour period before surgery or were scheduled to receive antiemetics not included in the study dosing scheme during the evaluation period were also excluded.

The first dose of rescue antiemetic medication could be administered when medically indicated, at physician discretion, or at any time on the patient's request. During the 48-hour assessment phase, episodes of nausea or emesis that resulted in the administration of rescue medication were considered treatment failures rather than adverse events (AEs) or serious adverse events (SAEs) and were captured in the assessments of emesis and nausea in the patient diary unless the severity was greater than expected. The institutional review board or ethics committee at each institution approved the protocol, and written informed consent was obtained from each patient before the performance of any study-specific procedures.

STUDY DESIGN

Patients were randomized to 1 of 2 treatment arms. Patients in cohort A received an oral placebo for casopitant approximately 60 minutes before and standard IV ondansetron, 4 mg (for 2-5 minutes), immediately before the induction of anesthesia. Patients in cohort B received oral casopitant, 50 mg, approximately 60 minutes before and IV ondansetron, 4 mg (for 2-5 minutes), immediately before the induction of anesthesia.

The primary objective of this study was to determine the proportion of patients who achieved a complete response (defined as no vomiting, retching, or rescue therapy during the first 24 hours after the placement of the last suture or last staple). On the basis of phase 2 data, assuming a 40.0% complete response rate for cohort A (IV ondansetron, 4 mg, only) at 24 hours, 231 patients per arm were expected to be required to show a 15.0% absolute difference in complete response rates between the 2 treatment arms with 90.0% power and a 2-sided level of significance of .05.

Secondary objectives included analyzing the following: (1) the severity of nausea experienced by patients, as assessed by a 0- to 10-point Likert scale and a categorical scale (none, mild, moderate, or severe) analyzed using a nonzero correlation test; (2) time to first emetic event, defined as the time from placement of the last suture or staple to the first emetic episode and summarized using Kaplan-Meier estimates; (3) time to first antiemetic rescue medication, defined as the time from placement of the last suture or staple to the first use of antiemetic rescue medication and summarized using Kaplan-Meier estimates; (4) patient satisfaction with the prophylactic antiemetic regimens and their willingness to use the same treatment regimen for future surgical procedures, as assessed by the patient satisfaction assessment in the patient diary; (5) safety and tolerability of the antiemetic regimens and AE reporting; (6) proportion of patients experiencing complete protection, defined as no vomiting, retching, or rescue therapy, and maximum nausea score less than 3 on the Likert scale; (7) proportion of patients experiencing total control, defined as no vomiting, retching, or rescue therapy, and a maximum nausea score less than 1 on the Likert scale; (8) proportion of patients experiencing no vomiting, where vomiting was defined as vomit or retch, but including patients who received rescue therapy; (9) proportion of patients experiencing significant nausea, defined as a maximum nausea score of 3 or higher on the Likert scale for nausea from all nausea assessments; (10) proportion of patients experiencing nausea, defined as a maximum nausea score of 1 or higher on the Likert scale for nausea from all nausea assessments, with maximum nausea score analyzed using

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Table 1. Demographics of Study Patients[a]

Demographic	Cohort A (Ondansetron Hydrochloride Only) (n=229)	Cohort B (Casopitant Mesylate Plus Ondansetron) (n=227)	Total
Age, y			
Mean (SD)	44.8 (12.44)	44.4 (12.19)	44.6 (12.30)
Median (range)	44 (18-79)	44 (18-83)	44 (18-83)
Height, cm			
Mean (SD)	161.3 (8.74)	162.8 (9.98)	162.0 (9.40)
Median (range)	161 (79-183)	162 (65-194)	162 (65-194)
Weight, kg			
Mean (SD)	70.6 (17.05)	72.3 (17.55)	71.5 (17.30)
Median (range)	67 (37-154)	69 (41-128)	68 (37-154)
Race, No. (%)			
African American or African	20/236 (8.5)	19/233 (8.2)	39/469 (8.3)
American Indian or Alaskan Native and white	1/236 (0.4)	1/233 (0.4)	2/469 (0.4)
Asian	50/236 (21.2)	46/233 (19.7)	96/469 (20.5)
Central or South Asian	5/236 (2.1)	7/233 (3.0)	12/469 (2.6)
Japanese, East Asian, or Southeast Asian	45/236 (19.1)	39/233 (16.7)	84/469 (17.9)
Native Hawaiian or other Pacific Islander	0	1/233 (0.4)	1/469 (0.2)
White	165/236 (69.9)	166/233 (71.2)	331/469 (70.6)
American Society of Anesthesiologists Physical Status Classification, No. (%)			
P1 (healthy)	94/242 (38.8)	87/242 (36.0)	181/484 (37.4)
P2 (mild systemic disease)	145/242 (59.9)	152/242 (62.8)	297/484 (61.4)
P3 (severe systemic disease)	2/242 (0.8)	1/242 (0.4)	3/484 (0.6)
Total surgery time, min			
Mean (SD)	92.1 (56.96)	87.7 (50.39)	NA
Median (range)	77 (10-414)	77 (14-270)	NA

Abbreviation: NA, not applicable.
[a] Percentages do not total 100 because of rounding.

a Wilcoxon rank sum test; and (11) proportion of patients receiving rescue medication. If a patient withdrew prematurely during the first 48 hours and did not have an emetic event or take rescue medication, the time of withdrawal was considered to be the time to first emetic episode or the time to first use of antiemetic rescue medication, and the patient's data were censored from that time point.

For the primary analysis, testing was conducted at a .05 level of significance. The Cochran-Mantel-Haenszel test was used to make comparisons. The odds ratios (ORs) are presented along with the associated 95% confidence intervals (CIs). Complete response in the 24- to 48-hour and 0- to 48-hour periods was analyzed as described for the primary efficacy analysis. If the primary objective was deemed significant, the following secondary objectives were tested hierarchically: no vomiting, complete protection (defined as complete response with no significant nausea), maximum nausea score, and total control (defined as complete response with no nausea). Each secondary objective used the prespecified hierarchy at the .05 level of significance with 95% CI.

All objectives (except safety, health outcomes, and time-to-event end points) were assessed in the following time windows: 0 to 24 hours, 24 to 48 hours, and 0 to 48 hours after placement of the last suture or staple. Health outcomes were assessed at 48 hours only. Nausea was also assessed in the following time windows: 0 to 2 hours and 0 to 6 hours. Safety was also assessed at days 6 to 10.

The primary population of interest was the modified intent-to-treat (ITT) population, which was used to perform the efficacy analysis. This population was the subset of the ITT population that received any investigational product and underwent surgery. The safety population was a subset of the ITT population that received an investigational product (casopitant or placebo).

RESULTS

STUDY POPULATION

Forty-three centers in 11 countries participated in this global study. Between March 20 and August 31, 2006, 484 patients were enrolled. Demographic characteristics were well balanced among the treatment groups (**Table 1**). The most frequently reported surgery types were hysterectomy (119 patients; 24.6%), cholecystectomy (77 patients; 15.9%), breast operation (44 patients; 9.1%), thyroid operation (34 patients; 7.0%), and bilateral salpingo-oophorectomy (12 patients; 2.5%).

In total, 456 patients (94.2%) completed the study: 229 (94.6%) in cohort A and 227 (93.8%) in cohort B. The reasons for the premature withdrawal of the 28 patients were as follows: 7 were lost to follow-up (3 [1.3%] in cohort A and 4 [1.8%] in cohort B), 3 had protocol violations (2 [0.9%] in cohort A and 1 [0.4%] in cohort B), 5 decided to withdraw (1 [0.4%] in cohort A and 4 [1.8%] in cohort B), and 13 withdrew because of other reasons (7 [3.1%] in cohort A and 6 [2.6%] in cohort B), including canceled surgery (4 in cohort A and 3 in cohort B), closed to recruitment (1 in each group), and treatment failure (1 in cohort A).

PRIMARY EFFICACY DATA

A significantly greater proportion of patients in the casopitant plus ondansetron group achieved the primary ob-

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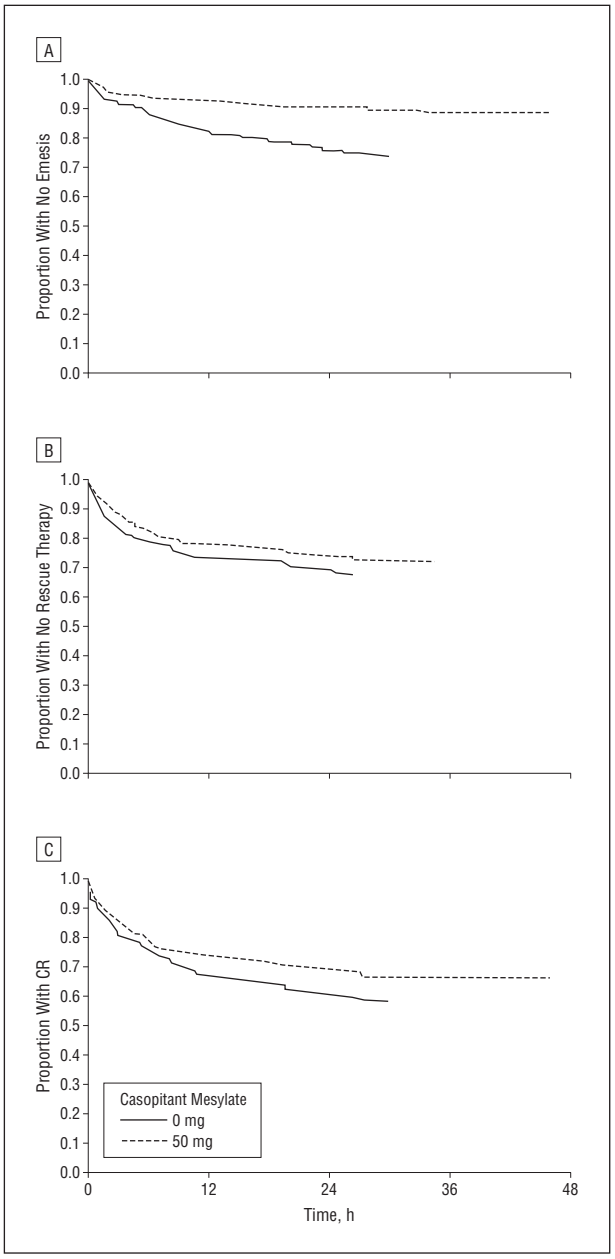

Figure. Kaplan-Meier curves. A, Time from last suture or staple to first emetic episode; B, time from last suture or staple to first rescue medication; and C, time from last suture or staple to first complete response (CR) failure.

jective of complete response (no vomiting, retching, or rescue therapy) during 0 to 24 hours (160/233 [68.7%]) compared with the ondansetron-only group (138/235 [58.7%]; OR, 1.54; 95% CI, 1.05-2.25; $P=.03$). In the supportive analysis of the ITT population, there was also a treatment difference between the casopitant plus ondansetron group (66.0%) and the ondansetron-only group (57.0%) for complete response during 0 to 24 hours ($P=.04$).

SECONDARY EFFICACY DATA

The difference between groups in complete response from 24 to 48 hours (163/233 [70.0%] in the casopitant plus ondansetron group vs 149/235 [63.4%] in the ondansetron-only group; OR, 1.34; 95% CI, 0.91-1.98; $P=.14$) was not significant. There was a statistically significant treatment difference in favor of the casopitant plus ondansetron group for patients with no vomiting during 0 to 24 hours (209/233 [89.7%] in the casopitant plus ondansetron group vs 176/235 [74.9%] in the ondansetron-only group; OR, 0.34; 95% CI, 0.20-0.57; $P<.001$). No statistically significant treatment difference was observed between the ondansetron-only group (102/235 [43.4%]) and the casopitant plus ondansetron group (120/233 [51.5%]) for complete protection during 0 to 24 hours (OR, 1.39; 95% CI, 0.96-2.01; $P=.08$). As a result, the third and fourth hypotheses, for maximum nausea score and total control, were not tested. Although no statistically significant treatment difference was observed between the ondansetron-only group and the casopitant plus ondansetron group for severity of nausea as measured by the Likert or categorical scales during 0 to 24 hours, there appeared to be a smaller proportion of patients in the casopitant plus ondansetron group (8.6%) reporting severe nausea compared with the ondansetron-only group (16.2%).

Time to first emetic episode was different between the ondansetron-only group and the casopitant plus ondansetron group, with the first emetic episode occurring later in the casopitant plus ondansetron group. The hazard ratio for the risk of emesis at any given time, relative to the risk of the patients who received only ondansetron, was 0.414 (95% CI, 0.265-0.646) (**Figure**, A).

Rescue medication use was reported by 31.0% of patients in the ondansetron-only group and 26.0% in the casopitant plus ondansetron group during 0 to 24 hours, by 6.0% in both groups during 24 to 48 hours, and by 33.0% in the ondansetron-only group and 29.0% in the casopitant plus ondansetron group during 0 to 48 hours. No difference was observed in the time to first rescue medication use. The hazard ratio for the risk of rescue medication at any given time, relative to the risk of the patients who received only ondansetron rescue, was 0.841 (95% CI, 0.606-1.167) (Figure, B). In a post hoc analysis, Kaplan-Meier curves were produced for time to first complete response failure (Figure, C). The trend was as expected and was consistent with the overall clinical conclusion of benefit of casopitant plus ondansetron over ondansetron alone.

SAFETY AND HEALTH OUTCOMES DATA

Of the 472 patients in the safety population, 237 patients were randomized in the ondansetron-only group and 235 patients in the casopitant plus ondansetron group. Three patients in the ondansetron-only group and 2 in the casopitant plus ondansetron group received an investigational product but were not recorded as having received ondansetron study medication.

At least 1 AE was reported during the study by 182 patients (38.6%). The most frequently reported AE irrespective of causality was constipation, which occurred in 25 patients overall (5.3%). The AE profiles were similar in the 2 treatment groups (**Table 2**). However, constipation and hypotension were reported in a greater proportion of patients in the casopitant group than in the ondansetron-only group. Twenty-seven patients (5.7%) had hypotension or procedural hypotension reported as an AE: 10 patients in the ondansetron-only group and

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17 in the casopitant plus ondansetron group. None of these was classed as an SAE. Twenty-seven patients (5.7%) had at least 1 AE that was considered possibly related to the investigational product by the investigator, with similar profiles in both treatment groups.

Most AEs were of mild or moderate intensity, and the treatment groups were balanced with regard to AE profile by intensity. Twelve patients in the study (2.5%) experienced at least 1 AE of severe intensity, 6 patients in each group. The most frequently reported AEs of severe intensity were constipation, occurring in 2 patients (0.4%) in the casopitant plus ondansetron group, and musculoskeletal pain, occurring in 1 patient (0.2%) in each group. Eleven patients (2.3%) had at least 1 SAE reported in this study, but none of the SAEs were fatal or considered to be related to the investigational product by the investigator.

Patient satisfaction during 0 to 48 hours appeared to be similar in the 2 treatment groups. This also appeared to be true regarding patient willingness to use the same regimens for future surgical procedures.

Table 2. Adverse Events Irrespective of Causality Reported in More Than 1% of Patients in Either Treatment Group (Safety Population)

	No. (%) of Patients	
Adverse Event	Cohort A (Ondansetron Hydrochloride Only) (n=237)	Cohort B (Casopitant Mesylate Plus Ondansetron) (n=235)
Any event	87 (36.7)	95 (40.4)
Constipation	8 (3.4)	17 (7.2)
Flatulence	12 (5.1)	11 (4.7)
Hypotension	8 (3.4)	15 (6.4)
Headache	11 (4.6)	8 (3.4)
Anemia	5 (2.1)	6 (2.6)
Cough	5 (2.1)	5 (2.1)
Insomnia	4 (1.7)	6 (2.6)
Nausea	4 (1.7)	6 (2.6)
Pruritus	5 (2.1)	4 (1.7)
Urinary retention	3 (1.3)	5 (2.1)
Hypertension	5 (2.1)	2 (0.8)
Diarrhea	4 (1.7)	2 (0.8)
Procedural hypotension[a]	2 (0.8)	2 (0.8)
Liver function test result abnormal[b]	7 (3.0)	8 (3.4)

[a] Included herein to present a more complete picture of hypotension.
[b] Indicates an increased alanine aminotransferase level, an increased aspartate aminotransferase level, an increased transaminase level and/or abnormal blood or liver function test results. Patients for whom more than 1 adverse event was reported (eg, increased alanine aminotransferase level and increased aspartate aminotransferase level reported as separate events) are counted once. During the 48-hour assessment phase, episodes of nausea or emesis that resulted in the administration of rescue medication were considered treatment failures rather than adverse events or serious adverse events and were captured in the assessments of emesis and nausea in the patient diary, unless the severity was greater than expected.

COMMENT

In this phase 3 study, the primary end point of complete response during the first 24 hours after surgery under general anesthesia was achieved in a significantly greater proportion of patients in the casopitant plus ondansetron group compared with the ondansetron-only group for the primary efficacy (modified ITT) population ($P=.03$), with a similar difference noted in the supportive analysis of the ITT population. The benefit of casopitant treatment appeared to persist during the 48 hours, although it was statistically significant only for the first 24-hour period.

In addition, a statistically significant decrease was noted in the proportion of patients reporting vomiting in the casopitant plus ondansetron group compared with the ondansetron-only group. The effect of casopitant on the end point of no vomiting appears more robust than the effect on complete response. A possible explanation for this outcome is that complete response required the patient to have no vomiting, retching, or rescue medication. It is possible that some patients required rescue medication for severe nausea, thus affecting the results for complete response because casopitant is an antiemetic drug and is therefore expected to be less effective against nausea. Formal hypothesis testing was not performed on the nausea end points because of the lack of benefit of casopitant for complete protection (no vomiting, retching, or rescue medication and no significant nausea) in this study.

The demonstrated superiority of casopitant in combination with ondansetron compared with ondansetron only was particularly noteworthy, considering the proportion of patients achieving a complete response (68.7% vs 58.7%, respectively) was higher than anticipated in the sample-size calculations (which had assumed a 40.0% complete response rate for the ondansetron-only group at 24 hours). A possible explanation for this is that many of the operations were shorter than expected and anesthesia times were less than the 1 hour required by the protocol. Duration of surgery has been shown to correlate with PONV risk.[4] Analyses of the efficacy results categorized by duration of anesthesia are not available for this study. However, the time of dosing 1 hour before anesthesia, the relatively short time to maximal concentration of casopitant after oral administration (<2 hours), the duration of anesthesia, and the time to first event suggest that most patients will have the opportunity to fully benefit from casopitant treatment even with short durations of anesthesia. In addition, the entry criteria in the phase 2 studies were changed for the current analysis so that there was no upper age limit, patients were not required to be premenopausal or perimenopausal (a possible risk factor), the definition of *nonsmoker* was relaxed to include those who had not smoked for 6 months and patients were permitted 2 or fewer cigarettes per week, and anesthetic regimens were not specified but rather only were required to be "balanced-general" according to institutional practices. All these factors would tend to increase the proportion of patients achieving complete response.[4,14]

The significant protection against PONV noted in patients receiving casopitant in combination with ondansetron observed in this study is additionally notable for occurring in a high-risk population in whom PONV is anticipated in up to 80.0% of cases in the absence of effective antiemetic therapy.[4] In addition, eligible operations were restricted to those with a high risk of PONV.[4]

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The selection of the 50-mg oral dose of casopitant was based on the results of a phase 2 study,[15] which showed that oral casopitant in combination with ondansetron was clinically effective and well tolerated. In the current analysis, casopitant mesylate at 50 mg was also determined to be well tolerated. The AE profiles were similar in the 2 treatment groups, but hypotension or procedural hypotension was reported in a smaller proportion of patients in the ondansetron-only group (4.2%) than in the casopitant plus ondansetron group (7.2%). Because perioperative events may have occurred before, during, or after surgery and the exact time of hypotension was not recorded, it was thought more appropriate to look at the hypotension and procedural hypotension events in combination rather than considering them as distinct events.

There were no notable differences in clinical laboratory hematology and biochemistry results or in vital signs and electrocardiography results among treatment groups. There were no deaths in this study, and none of the SAEs observed were considered by the investigator to be related to the investigational product or study medication. There were no AEs that led to premature discontinuation from the study.

A limitation of the study was that there was no placebo arm in which no emetogenic medication was administered. Because nausea and vomiting are highly likely to occur in this high-risk patient population and perioperative antiemetic prophylaxis is the standard of care, a placebo arm would not have been acceptable or appropriate.

In conclusion, the results of this pivotal phase 3 study demonstrate the efficacy and tolerability of the 50-mg oral casopitant dose, in combination with IV ondansetron, 4 mg, in patients at high risk for PONV. The combined treatment was superior to ondansetron alone.

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