Synopsis

Identifier: HM2005/00235/00 **Study Number:** NKO101287

Title: A Multicenter, Randomized, Double-blind, Double-Dummy, Placebo-controlled, Parallel Group, Phase II Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Oral (25mg) and Intravenous (3mg and 18mg) Formulations of the Neurokinin-1 Receptor Antagonist, GW597599, When Administered with Intravenous Ondansetron Hydrochloride for the Prevention of Post-Operative Nausea and Vomiting (PONV) and Post-Discharge Nausea and Vomiting (PDNV) in Female Subjects with Known Risk Factors for PONV Who are Undergoing Surgical Procedures Associated with an Increased Emetogenic Risk

Investigator(s): This was a multicenter study.

Study center(s): A total of 49 centers randomized subjects for this study: 13 in the US, seven in Canada, six in Australia, four each in Belgium and the Czech Republic, three each in Poland and the Netherlands, two each in the UK, Finland, Chile, and South Africa, and one in Turkey.

Publication(s): None at the time of this report.

Study Period: 21 December 2004 to 21 April 2006.

Phase of Development: II

Objectives:

The primary objective of this study was to determine whether a single oral or IV dose of vestipitant, when administered in combination with IV ondansetron hydrochloride, improves the prophylaxis against emesis (defined as vomiting or retching) during the first 24 hrs following emergence from anesthesia in female subjects with known risk factors for post-operative nausea and vomiting (PONV) who were undergoing surgical procedures associated with increased emetogenic risk.

The secondary objectives of this study were:

- To determine, within this study population, whether a single dose of oral or IV vestipitant in combination with intravenous ondansetron hydrochloride:
    - Improves the prophylaxis against emesis measured daily for up to 120 hrs following the emergence from anesthesia.
    - Improves the prevention of nausea during the first 24 hrs (as assessed at 2, 6, and 24 hrs) and measured daily for up to 120 hrs following the emergence from anesthesia.
- To evaluate the safety profile of single dose vestipitant when administered in combination with ondansetron hydrochloride in this study population.

- To quantify the impact of single dose vestipitant when administered in combination with ondansetron hydrochloride on daily life activities, as assessed by a Functional Living Index - Emesis (FLIE) questionnaire, in this study population.
- To assess subject satisfaction of single dose vestipitant in the control of PONV and post-discharge nausea and vomiting (PDNV).
- To evaluate subject-reported pain (assessed at 2, 6, and 24 hours for Day 1, and at each subsequent 24-hr evaluation period up to 120 hrs following emergence from anesthesia) in this study population.
- To evaluate pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of oral and IV vestipitant.

Methodology: A Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of oral and IV vestipitant administered in combination with ondansetron hydrochloride (4mg IV) for the prevention of PONV and PDNV in female subjects with known risk factors for PONV who were undergoing surgical procedures that were associated with an increased emetogenic risk.

Subjects were stratified by menopausal status (i.e., pre-menopausal or peri-menopausal) and the type of surgical procedure (i.e., gynecologic or cholecystectomy). Surgical procedures were limited to laparoscopic/laparotomic gynecological surgical procedures or laparoscopic cholecystectomy that was scheduled for between 1 and 3 hrs in duration.

Subjects eligible for this study were randomized to one of the four treatment groups. Investigational antiemetic drugs were administered prior to induction of anesthetics on the day of surgery only. Four parallel treatment groups were:

- Group A: oral vestipitant-matched placebo, IV ondansetron HCl 4mg, and IV vestipitant-matched placebo.
- Group B: oral vestipitant 25mg, IV ondansetron HCl 4mg, and IV vestipitant-matched placebo.
- Group C: oral vestipitant-matched placebo, IV ondansetron HCl 4mg, and IV vestipitant 3mg.
- Group D: oral vestipitant-matched placebo, IV ondansetron HCl 4mg, and IV vestipitant 18mg.

Pre-operative and intraoperative surgical anesthestics/neuromuscular blockade and post-operative/subsequent analgesics were standardized as general balanced anesthesia, and were administered in accordance to the protocol in addition to local and institutional requirements.

Number of subjects:

Number of Subjects	Ond	Ond/Ves 3mg IV	Ond/Ves 18mg IV	Ond/Ves 25mg Oral
Planned, N	156	156	156	156
Randomized, N	157	156	154	154
Completed, n (%)	149 (95)	137 (88)	143 (93)	142 (92)
Total Number of Subjects Withdrawn, n (%)	8 (5)	19 (12)	11 (7)	12 (8)
Withdrawn due to AEs, n (%)	0	1 (<1)	0	0
Withdrawn due to Lack of Efficacy, n (%)	0	0	0	0
Withdrawn for Other Reasons, n (%)	8 (5)	18 (12)	11 (7)	12 (8)

AEs = adverse events; Ond = Ondansetron HCl; Ves = Vestipitant. Ondansetron HCl dosed at 4mg IV

Diagnosis and main criteria for inclusion: Eligiblility was limited to non-pregnant females aged 18 to 55 years who had provided a written informed consent and met all other inclusion and exclusion criteria, including; pre-menopausal or peri-menopausal status, non-smoker for at least 12 months, presented with an American Society of Anesthesiologists (ASA) Physical Status of I or II on the day of surgery, had a history of PONV and/or motion sickness, and was scheduled to undergo a laparoscopic/laparotomic gynecological surgical procedure or laparoscopic cholecystectomy (planned for 1 to 3 hrs in duration) involving a standardized analgesic and anesthetic regimen.

Treatment administration: Study medications (ondansetron hydrochloride injection, vestipitant injection [1mg/mL and 5mg/mL], vestipitant tablets, and matching placebo [both oral and IV formulations]) were supplied by GSK.

Criteria for evaluation: The primary endpoint was complete antiemetic response rate, defined as no vomiting, retching, rescue therapy, or premature discontinuation from the study during the first 24-hour evaluation period following the emergence from anesthesia. Secondary efficacy variables included scheduled assessments for antiemetic response, nausea, pain, quality of life (QoL), and subject satisfaction 120 hrs post-emergence from anesthesia. Scheduled PK samples were obtained up to 24 hrs following vestipitant dosing. Safety evaluation included routine assessments of vital signs, serum chemistries, and hematology parameters, electrocardiograms (ECG), adverse events (AEs), serious adverse events (SAEs), and assessment of time to awakening from anesthesia and time to readiness for discharge.

Statistical methods: Sample size assumptions were based on a complete response rate of 56% for placebo and a 20% improvement for the 25mg oral dose or 18mg IV dose. Assuming a 12% non-evaluable rate, the total ITT population was estimated to be 156 subjects per arm with a total enrollment of 624 subjects to be randomized to one of the four treatment groups. The Cochran-Mantel-Haenszel test was used to compare complete responses. The treatment comparisons were performed in a hierarchical fashion, as follows: Step I, Treatment Group B vs. Group A and Treatment Group D vs. Group A; Step II, Treatment Group C vs. Group A. The Step I comparisons were tested at a 2.5% level of significance. If the result of one of these comparisons was significant ($p<0.025$), then the Step II comparison was to be carried out at the 5% level of significance. P-values for secondary endpoints were provided for descriptive purposes only.

The intent-to-treat (ITT) population was defined as all subjects who were randomized. The ITT population was used to analyze efficacy data. The Per-Protocol (PP) population comprised all randomized and treated subjects who complied closely with the protocol and was used to provide a supplementary analysis of the primary endpoint. The safety population comprised all subjects who received any study medication.

Adverse events and SAEs were summarized by system organ class and relationship to study medication. Adverse events were also summarized according to intensity (mild, moderate or severe), and AEs and SAEs that led to withdrawal from the study were described.

Summary:

Study Population: 621 female subjects with known risk factors for PONV who were undergoing surgical procedures that were associated with an increased emetogenic risk were enrolled into the study; 571 (92%) subjects completed the study.

Primary Efficacy: The complete response rate (0 to 24 hrs) was statistically significant in favor of the vestipitant 25mg oral treatment group compared with ondansetron hydrochloride alone (60% vs. 42%; odds ratio 2.11; 97.5% CI: 1.25, 3.55; p=0.0013). The complete response rate was higher in the vestipitant 18mg IV treatment group compared with ondansetron hydrochloride alone (55% vs. 42%; odds ratio: 1.64; 97.5% CI: 0.98, 2.75; p=0.0287); this result was not statistically significant at the 2.5% level. As one of these first two comparisons was statistically significant, a comparison of vestipitant 3mg IV dosing versus ondansetron hydrochloride alone was performed at the 5% significance level. The complete response rate was marginally higher in the vestipitant 3mg IV treatment group compared with ondansetron hydrochloride alone, but the difference was not statistically significant (46% vs. 42%; odds ratio 1.26; 95% CI: 0.79, 2.00; p=0.4610).

Secondary Efficacy: Differences between treatment groups for secondary efficacy endpoints were not formally tested.

Complete response rates: The proportion of subjects achieving a complete response was higher for all active vestipitant plus ondansetron hydrochloride treatment groups compared with ondansetron hydrochloride alone for each assessment period up to 120 hrs post-emergence from anesthesia (see following table).

Complete Response Rate	Treatment Group			
	Ond N=157	Ond/ Ves 3mg IV N=156	Ond/ Ves 18mg IV N=154	Ond/ Ves 25mg Oral N=154
0 to 48 hrs				
Rate, %	39	43	49	58
Odds Ratio (95% CI)		1.26 (0.79, 2.01)	1.48 (0.88, 2.50)	2.23 (1.32, 3.77)
0 to 120 hrs				
Rate, %	38	43	48	57
Odds Ratio (95% CI)		1.26 (0.79, 2.01)	1.47 (0.87, 2.49)	2.18 (1.29, 3.68)

Ond = Ondansetron HCl; Ves = Vestipitant. Ondansetron HCl dosed at 4mg IV

Complete Protection was defined as no vomiting, no retching, no rescue therapy, no premature withdrawal, and maximum nausea <25 on the VAS scale. A greater proportion of subjects achieving complete protection was observed for all active vestipitant plus ondansetron hydrochloride treatment groups compared with ondansetron hydrochloride alone at all assessment periods up 120 hrs post-emergence from anesthesia (see table below). The improvement over ondansetron hydrochloride alone was greatest in the vestipitant 25mg oral treatment group.

Complete Protection Rate	Treatment Group			
	Ond N=157	Ond/ Ves 3mg IV N=156	Ond/ Ves 18mg IV N=154	Ond/ Ves 25mg Oral N=154
0 to 24 hrs				
Rate, %	24	32	34	41
Odds Ratio (95% CI)		1.70 (1.02, 2.85)	1.79 (1.00, 3.20)	2.24 (1.27, 3.93)
0 to 48 hrs				
Rate, %	21	29	30	37
Odds Ratio (95% CI)		1.71 (1.01, 2.90)	1.65 (0.90, 3.03)	2.20 (1.23, 3.94)
0 to 120 hrs				
Rate, %	18	29	28	36
Odds Ratio (95% CI)		1.93 (1.12, 3.33)	1.80 (0.97, 3.37)	2.55 (1.39, 4.67)

Ond = Ondansetron HCl; Ves = Vestipitant
Ondansetron HCl dosed at 4mg IV

Total Control was defined as no vomiting, no retching, no rescue therapy, no premature withdrawal, and a maximum nausea <5 on the VAS scale. A greater proportion of subjects achieved total control in all active vestipitant plus ondansetron hydrochloride treatment groups when compared with ondansetron hydrochloride alone during all assessment periods up to 120 hrs post-emergence from anesthesia (see table below). The improvement over ondansetron hydrochloride alone was greatest in the vestipitant 25mg oral treatment group.

Total Control Rate	Treatment Group			
	Ond N=157	Ond/ Ves 3mg IV N=156	Ond/ Ves 18mg IV N=154	Ond/ Ves 25mg Oral N=154
0 to 24 hrs				
Rate, %	20	25	27	32
Odds Ratio (95% CI)		1.41 (0.82, 2.43)	1.52 (0.82, 2.81)	1.88 (1.04, 3.42)
0 to 48 hrs				
Rate, %	17	22	24	29
Odds Ratio (95% CI)		1.47 (0.83, 2.61)	1.56 (0.82, 2.98)	1.92 (1.03, 3.60)
0 to 120 hrs				
Rate, %	13	22	22	27
Odds Ratio (95% CI)		1.85 (1.00, 3.42)	1.87 (0.93, 3.74)	2.33 (1.19, 4.59)

Ond = Ondansetron HCl; Ves = Vestipitant
Ondansetron HCl dosed at 4mg IV

No Vomiting: The majority of subjects across all treatment groups did not experience vomiting. Greater proportions of subjects with no vomiting were observed for all active vestipitant plus ondansetron hydrochloride treatment groups compared with ondansetron hydrochloride alone during all assessment periods up to 120 hrs post-emergence from anesthesia (see following table).

No Vomiting	Treatment Group			
	Ond N=157	Ond/ Ves 3mg IV N=156	Ond/ Ves 18mg IV N=154	Ond/ Ves 25mg Oral N=154
0 to 24 hrs				
Rate, %	67	72	87	82
Odds Ratio (95% CI)		1.32 (0.81, 2.17)	3.27 (1.69, 6.32)	2.21 (1.20, 4.06)
0 to 48 hrs				
Rate, %	66	71	83	80
Odds Ratio (95% CI)		1.31 (0.81, 2.14)	2.56 (1.37, 4.77)	2.07 (1.14, 3.75)
0 to 120 hrs				
Rate, %	66	70	81	79
Odds Ratio (95% CI)		1.23 (0.76, 2.00)	2.25 (1.23, 4.14)	1.92 (1.07, 3.46)

Ond = Ondansetron HCl; Ves = Vestipitant
Ondansetron HCl dosed at 4mg IV

No Significant Nausea: The majority of subjects across all treatment groups did not experience significant nausea during the first 2-hour assessment period. Greater proportions of subjects with no significant nausea were observed for all active vestipitant plus ondansetron hydrochloride treatment groups compared with the ondansetron hydrochloride alone treatment group for any of assessment periods up to 120 hrs.

No Significant Pain: The majority of subjects experienced significant pain across all treatment groups at all of the assessment periods up to 120 hrs. The proportions of subjects who experienced significant pain were comparable across all treatment groups for the 2- and 6-hr assessment periods. Smaller proportions of subjects experiencing significant pain were observed for all active vestipitant plus ondansetron hydrochloride

treatment groups compared with the ondansetron hydrochloride alone treatment group during the 24-, 48- and 120-hr assessment periods.

Time to Emesis and Time to Rescue: Because of the high number of censored subjects for all active vestipitant plus ondansetron hydrochloride treatment groups, median values could not be calculated. However, the proportion of subjects experiencing an emesis event was generally lower in the active vestipitant groups (18.8% to 30.1%) compared with the ondansetron hydrochloride alone treatment group (34.4%). Fewer subjects receiving vestipitant 3mg IV (31.4%) or vestipitant 25mg oral (24%) required rescue therapy compared with those receiving vestipitant 18mg IV (39%) or ondansetron hydrochloride alone (37.6%).

Safety: A total of 196 subjects (33%) reported at least one AE. Those reported in at least 3% of subjects in any treatment group are shown in the table below. The highest incidence of hepatic-enzyme-related AEs was observed in the ondansetron hydrochloride alone treatment group.

	Treatment Group, n (%)			
Preferred Term	Ond N=153	Ond/ Ves 3mg IV N=145	Ond/ Ves 18mg IV N=146	Ond/ Ves 25mg Oral N=145
Any event	51 (33)	48 (33)	55 (38)	42 (29)
ALT increased	9 (6)	3 (2)	3 (2)	4 (3)
Headache	5 (3)	4 (3)	5 (3)	4 (3)
Pyrexia	8 (5)	2 (1)	6 (4)	1 (<1)
Dizziness	4 (3)	5 (3)	1 (<1)	5 (3)
Constipation	2 (1)	2 (1)	4 (3)	6 (4)
Pruritus	4 (3)	2 (1)	4 (3)	3 (2)
AST increased	5 (3)	1 (<1)	2 (1)	2 (1)
Hepatic enzyme increased	2 (1)	2 (1)	4 (3)	-
Procedural hypotension	2 (1)	2 (1)	-	4 (3)
Procedural complication	4 (3)	1 (<1)	1 (<1)	1 (<1)
Diarrhea	-	1 (<1)	1 (<1)	4 (3)

Ond = Ondansetron HCl; Ves = Vestipitant; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase
Ondansetron HCl dosed at 4mg IV

The majority of AEs were considered by the investigator to be mild or moderate in severity as defined in the protocol. Thirteen subjects (2%) had at least one AE considered by the investigator to be severe. The highest incidence of severe AEs was observed in the vestipitant 18mg IV plus ondansetron hydrochloride treatment group (5%). With the exception of vomiting (two subjects in the vestipitant 3mg IV plus ondansetron hydrochloride treatment group), none of these severe events occurred in more than one subject.

AEs considered by the investigator to be suspected or probably related to study medication were reported in 35 subjects (6%). The most frequent were ALT increased, AST increased, hepatic enzyme increased and headache.

There were no deaths reported. Serious adverse events were reported in 21 (4%) subjects. The highest incidence of SAEs was observed in the vestipitant 18mg IV plus ondansetron hydrochloride treatment group (9/146, 6%). Overall, the most common SAEs were surgical procedure related events: procedural pain (3 subjects overall), post procedural hemorrhage, procedural complication, and sepsis (two subjects each overall). Only one SAE was considered by the investigator to be related to study medication: a case of hepatic enzyme increased in a subject in the ondansetron hydrochloride alone treatment group.

Only one subject discontinued study medication due to an AE. This subject was receiving vestipitant 3mg IV plus ondansetron hydrochloride 4mg IV and had an AE of severe pelvic pain, considered by the investigator to be unrelated to study medication.

Changes from baseline in clinical chemistry and hematology values were seen during the study, but these changes were similar across treatment groups.

Pharmacokinetics/Pharmacodynamics: The IV and oral PK of vestipitant were simultaneously modeled. The oral bioavailability of vestipitant was estimated to be 70%, and systemic CL was estimated to be 33.6L/h (between-subject variability of 36%). The AUC of 25mg oral vestipitant was comparable to that of 18mg IV vestipitant; although, the Cmax was ~80% lower. The PK of vestipitant appeared dose-proportional and no clinically relevant covariates of vestipitant PK in this female patient population were evident, however, this patient population was not racially diverse.

PK/PD evaluation was performed using a graphical approach. As only one oral dose was studied, little exposure-response relationships were evident. Over the IV dose range studied (3 and 18mg); clear exposure response relationships were evident. Higher vestipitant concentrations produced by the higher dose level were correlated with no emesis (0 to 120 hrs) and no nausea; however, higher vestipitant concentrations were also correlated with increased use of rescue therapy (0 to 120 hrs). Overall, IV vestipitant exposure did not correlate with complete response (0 to 24 hrs).

Health Outcomes:

FLIE Scores: Similar mean FLIE scores were observed across the treatment groups at Baseline and at 120 hrs post-emergence from anesthesia period.

Subjects Satisfaction and Willingness: Between 65% and 72% of subjects in each treatment group were very satisfied/somewhat satisfied with study medication in preventing post-operative nausea and vomiting. Between 68% and 71% of subjects indicated that they definitely/probably would be willing to use the same antiemetic drug treatment regimen for future surgical procedure. The findings were similar across active treatment groups, with slightly higher percentages of subjects being ‘very satisfied’ or ‘definitely willing’ in the active vestipitant groups compared with ondansetron hydrochloride alone.

Conclusions: Complete response rates (0 to 24 hrs) were statistically significantly higher in the vestipitant 25mg oral group (60%) versus the the ondansetron alone group (42%). Complete response rates in the vestipitant 18mg IV group (55%) and the vestipitant 3mg

IV group (46%) were also higher than reported for ondasetron hydrochloride alone (42%), but neither of these comparisons reached statistical significance. All active doses and formulations of vestipitant were well tolerated by subjects in this patient population. The AUC following administration of 25mg oral and 18mg IV vestipitant were similar, although, the Cmax of oral vestipitant was ~80% lower and delayed by ~3-7 hours compared to IV vestipitant. High vestipitant exposures were correlated with reduced rates of emesis and nausea; however, increased use of rescue therapy was observed following IV administration. Vestipitant 25mg oral formulation in combination with the standard dose of ondansetron hydrochloride (4mg IV) provided enhanced protection against PONV in female subjects with known risk factors for PONV who were undergoing surgical procedures associated with increased emetogenic risk.

Date of Report: June 2007