The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: NKT102552

Title: A Phase III Multicenter, Randomized, Double-blind, Parallel Group Study to Evaluate the Safety and Efficacy of the 30mg Intravenous Formulation of the Neurokinin-1 Receptor Antagonist GW679769 for Prevention of Postoperative Nausea and Vomiting in Female Subjects at High Risk for Emesis.

Rationale: Post-operative nausea and vomiting (PONV) often occurs following local, regional, or general anesthesia and is the most frequently-reported patient complaint following anesthesia. The nucleus tractus solitarius (NTS) is presumed to be the primary site of action of emetic activity. Neurokinin, subtype 1 (NK-1) receptor occupancy in the striatal region is taken as a surrogate for assessing activity in the NTS. The purpose of this study was to investigate the safety and efficacy of the NK-1 receptor antagonist casopitant in combination with a single standard intravenous (IV) dose of ondansetron hydrochloride (Ond) in female subjects undergoing surgery who were at high risk of PONV.

Phase: III

Study Period: 22 March 2006 – 01 August 2006

Study Design: Multicenter, randomized, double-blind, active controlled, single dose, two-arm parallel group study.

Centers: Fifty-five centers in North America, Europe and Asia.

Indication: PONV.

Treatment: GW679769 (casopitant) 30mg or matching placebo, administered as a single IV dose approximately 15 minutes prior to induction of anesthesia; and single dose Ond 4mg IV administered immediately prior to induction of anesthesia.

Objectives: The primary objective of this study was to demonstrate the superiority of 30mg IV casopitant in combination with a single 4mg IV dose of Ond, over a single 4mg IV dose of Ond alone in the control of emesis during the first 24 hours following placement of the last suture/staple (as measured by complete response [CR]) in surgical subjects who were predicted to have a high risk of emesis.

Primary Outcome/Efficacy Variable: The proportion of subjects who achieved CR (defined as no vomiting, no retching and no rescue therapy for nausea and/or emesis during the first 24 hours following the placement of last suture/last staple).

Secondary Outcome/Efficacy Variables: Vomiting, complete protection (CR with no significant nausea), nausea, total control (CR with no nausea), rescue medication use, time to first emetic event, time to first rescue medication, health outcomes, safety and tolerability.

Statistical Methods: The primary efficacy analysis compared the treatment groups for CR (0–24 hours) in the Modified Intent-to-Treat (MITT) population, defined as randomized subjects who received any investigational product and had surgery. Testing was conducted at the 5% level of significance using the Cochran-Mantel-Haenszel test (stratified by anticipated intra-operative nitrous oxide use). P values, odds ratios and 95% confidence intervals (CIs) were reported. The ITT population, defined as all subjects who were randomized to treatment, was a supportive population for the primary efficacy endpoint.

Secondary endpoints (0–24 hours) were tested hierarchically in the following order: no vomiting; complete protection; maximum nausea score; and total control. Once a hypothesis failed to meet statistical significance, all subsequent hypotheses were not tested. Secondary efficacy analyses: 1) the Cochran-Mantel-Haenszel test was used for CR, complete protection, total control, vomiting, significant nausea, and nausea; 2) time to emesis and time to rescue were summarized using Kaplan-Meier estimates; 3) maximum nausea score was analyzed using a Wilcoxon Rank Sum test; 4) categorical nausea score was analyzed using a non-zero correlation test.

Summary statistics for safety and tolerability data were tabulated for the Safety population, defined as a subset of the ITT population that received investigational product (either casopitant or placebo).

Study Population: Female subjects aged ≥18 years, at high risk for developing PONV, scheduled to undergo one of the following procedures: breast surgery, orthopedic shoulder surgery, or thyroid surgery. The following laparoscopic or laparotomic procedures were also permitted: cholecystectomy, hysterectomy, or other gynecologic surgery. All surgeries were anticipated to involve general anesthesia of at least 1 hour duration. All subjects had the following Apfel significant risk factors: female gender; history of PONV and/or motion sickness; had not smoked or used tobacco for at least the previous 6 months; anticipated to receive postoperative opioids.

Number of Subjects:	**Ond Alone**	**Casopitant (+ Ond)**	**Total**
Planned, N	231	231	462
Randomized, N	258	256	514

Completed, n (%)	245 (95)	240 (94)	485 (94)
Total Number Subjects Withdrawn, N (%)	13 (5)	16 (6)	29 (6)
Withdrawn due to Adverse Events n (%)	0	1 (<1)	1 (<1)
Lost to Follow-Up, n (%)	2 (<1)	2 (<1)	4 (<1)
Protocol Violation, n (%)	0	1 (<1)	1 (<1)
Subject decided to withdraw, n (%)	5 (2)	6 (2)	11 (2)
Withdrawn for other reasons n (%)	6 (2)	6 (2)	12 (2)
Demographics	**Ond Alone**	**Casopitant (+Ond)**	**Total**
N (ITT)	258	256	514
Females: Males	All female	All female	All female
Mean Age, years (range)	46.4 (20–77)	45.2 (21–83)	45.8 (20–83)
Race, n (%)			
White	188 (73)	175 (68)	363 (71)
Asian	57 (22)	67 (26)	124 (24)
African American/African heritage	11 (4)	13 (5)	24 (5)
American Indian or Alaskan Native	2 (<1)	1 (<1)	3 (<1)
Primary Efficacy Results (MITT Population):			
	Ond Alone	**Casopitant (+Ond)**	
	(N=249)	**(N=244)**	
Complete response 0–24 hours, n/N (%)	133/249 (53)	169/244 (69)	
Cochran-Mantel-Haenszel test p value	0.0003		
Odds ratio (95% confidence interval)	1.96 (1.36, 2.84)		
Complete response by stratification			
Nitrous oxide anticipated, n/N (%)	74/132 (56)	88/130 (68)	
No nitrous oxide anticipated, n/N (%)	59/117 (50)	81/114 (71)	
Secondary Outcome Variables (MITT Population):			
	Ond Alone	**Casopitant (+Ond)**	
0–24 hour Time Period	**(N=249)**	**(N=244)**	
No vomiting, n (%)	168 (67)	220 (90)	
Odds ratio (95% confidence interval)		0.23 (0.14, 0.37)	
Complete protection, n (%)	100 (40)	120 (49)	
Odds ratio (95% confidence interval)		1.44 (1.01, 2.06)	
Maximum nausea score (Likert scale), mean (SD)	3.4 (3.7)	2.8 (3.3)	
Total control, n (%)	90 (36)	110 (45)	
Nausea (categorical scale), n (%)			
None	114 (46)	126 (52)	
Mild	39 (16)	45 (18)	
Moderate	54 (22)	49 (20)	
Severe	42 (17)	24 (10)	
24–48 hour Time Period	**Ond Alone**	**Casopitant (+Ond)**	
Complete response, n (%)	164 (66)	168 (69)	
No vomiting, n (%)	238 (96)	238 (98)	
Complete protection, n (%)	152 (61)	159 (65)	
Maximum nausea score (Likert scale), mean (SD)	0.9 (2.3)	0.6 (1.7)	
Total control, n (%)	145 (58)	156 (64)	
Nausea (categorical scale), n (%)			
None	207 (83)	213 (87)	
Mild	21 (8)	16 (7)	
Moderate	16 (6)	11 (5)	
Severe	5 (2)	4 (2)	
0–48 hour Time Period	**Ond Alone**	**Casopitant (+Ond)**	
Complete response, n (%)	130 (52)	160 (66)	
No vomiting, n (%)	166 (67)	217 (89)	

Complete protection, n (%)	93 (37)	114 (47)
Maximum nausea score (Likert scale), mean (SD)	3.6 (3.7)	3.0 (3.3)
Total control, n (%)	82 (33)	102 (42)
Nausea (categorical scale), n (%)		
None	105 (42)	118 (48)
Mild	44 (18)	44 (18)
Moderate	56 (22)	55 (23)
Severe	44 (18)	27 (11)
Time to first emetic episode	**Ond Alone**	**Casopitant (+Ond)**
Number of subjects with event, n (%)	83 (33)	27 (11)
Censored subjects, n (%)	166 (67)	217 (89)
Kaplan-Meier estimate, hours		
1st Quartile (95% CI)	9.8 (6.2, 19.8)	NE (NE, NE)
Median hours (95% CI)	NE (NE, NE)	NE (NE, NE)
3rd Quartile (95% CI)	NE (NE, NE)	NE (NE, NE)
NE=not estimable		
Time to first rescue medication use	**Ond Alone**	**Casopitant (+Ond)**
Number of subjects with event, n (%)	80 (32)	73 (30)
Censored subjects, n (%)	169 (68)	171 (70)
Kaplan-Meier estimate, hours		
1st Quartile (95% CI)	13.8 (6.2, 21.4)	23.6 (6.9, NE)
Median hours (95% CI)	NE (NE, NE)	NE (NE, NE)
3rd Quartile (95% CI)	NE (NE, NE)	NE (NE, NE)
NE=not estimable		
Health outcomes 0-48 hours	**Ond Alone**	**Casopitant (+Ond)**
Subject satisfaction with antiemetic regimen, n (%)		
Very satisfied	139 (56)	145 (59)
Somewhat satisfied	45 (18)	53 (22)
Neither satisfied nor dissatisfied	28 (11)	17 (7)
Somewhat dissatisfied	18 (7)	13 (5)
Very dissatisfied	8 (3)	1 (<1)
Subject willingness to use regimen for future surgical procedures, n (%)		
Definitely would be willing	118 (47)	142 (58)
Probably would be willing	69 (28)	53 (22)
Not certain	33 (13)	26 (11)
Probably would not be willing	10 (4)	6 (2)
Definitely would not be willing	8 (3)	2 (<1)

Safety Results: All AEs occurring after administration of the first dose of investigational product and on or before the final visit were reported, irrespective of whether they were considered drug related. SAEs that were related to study participation (e.g., procedures, invasive tests, etc.) or were related to a concurrent medication were collected and recorded from the time the subject consented to participate in the study until the subject was discharged.

	Ond Alone	**Casopitant (+Ond)**
Most Frequent Adverse Events – On-Therapy	**(N=249)**	**(N=244)**
Subjects with any AE(s), n(%)	114 (46)	118 (48)
Most Frequent AEs (≥3% of subjects in either group), n (%)		
Headache	13 (5)	12 (5)
Hypotension	8 (3)	11 (5)
Leukocytosis	9 (4)	7 (3)
Dizziness	5 (2)	10 (4)
Constipation	4 (2)	10 (4)
Nausea	7 (3)	7 (3)
Pruritus	6 (2)	8 (3)
Pyrexia	9 (4)	4 (2)
Aspartate aminotransferase increased	5 (2)	7 (3)
Bradycardia	2 (<1)	9 (4)

Procedural hypotension	7 (3)	3 (1)
Serious Adverse Events – On-Therapy	**Ond Alone**	**Casopitant (+Ond)**
Any non-fatal SAE, n (%) [n related to investigational product]	7 (3) [1]	9 (4) [2]
Angina pectoris	1 (<1) [0]	0
Cerebral arteritis	0 [0]	1 (<1) [1]
Deep vein thrombosis	1 (<1) [0]	0
Gallbladder cancer	0	1 (<1) [0]
Hepatic enzyme increased	0	1 (<1) [1]
Hypersensitivity	1 (<1) [1]	0
Hypotension	0	1 (<1) [0]
Ileus	0	1 (<1) [0]
Intra-abdominal hemorrhage	1 (<1) [0]	0
Jaundice	1 (<1) [0]	0
Menorrhagia	0	1 (<1) [0]
Myocardial ischemia	1 (<1) [0]	0
Operative hemorrhage	0	1 (<1) [0]
Psychotic disorder	0	1 (<1) [0]
Respiratory arrest	1 (<1) [0]	0
Traumatic hematoma	1 (<1) [0]	0
Urinary bladder rupture	0	1 (<1) [0]
Subjects with fatal SAEs, n (%)	0	0

Conclusion: This study showed that 133 (53%) subjects achieved CR (0–24 hours) in the placebo + Ond group and 169 (69%) in the casopitant + Ond group. In total, 114 (46%) subjects reported AEs in the placebo + Ond group and 118 (48%) in the casopitant + Ond group, with the most frequently reported AEs being headache and hypotension. Sixteen subjects (3%) reported SAEs, three of which were considered by the investigator to be possibly drug-related (hypersensitivity in the placebo + Ond group, and cerebral arteritis and increased hepatic enzyme in the casopitant + Ond group). There were no deaths in this study.