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: NKV101983

Title: A Phase II multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel group study of the safety and efficacy of the oral neurokinin-1 receptor antagonist, GW679769, when administered as 50mg, 100mg, and 150mg oral tablets in combination with ondansetron hydrochloride and dexamethasone for the prevention of chemotherapy-induced nausea and vomiting in cancer subjects receiving moderately emetogenic chemotherapy.

Rationale: This study was conducted to evaluate whether doses of GW679769 administered orally for three consecutive days improves the antiemetic efficacy of three day dosing of oral ondansetron hydrochloride and a single IV dose of dexamethasone in subjects with cancer receiving moderately emetogenic chemotherapy (MEC). Results of this study would support Phase III safety and efficacy studies in this setting.

Phase: II.

Study Period: 27 December 2004 to 27 December 2005.

Study Design: A multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel group study.

Centres: 99 study centers across 24 countries recruited subjects for this study.

Indication: Chemotherapy-induced nausea and vomiting.

Treatment: Subjects were randomly assigned to receive one of the following oral regimens beginning on study Day 1 of each treatment cycle prior to chemotherapy:

Group A: Ondansetron 8mg bid + placebo bid for 3 days
Group B: GW679769 50mg od + ondansetron 8mg bid for 3 days
Group C: GW679769 100mg od + ondansetron 8mg bid for 3 days
Group D: GW679769 150mg od + ondansetron 8mg bid for 3 days
Group E: GW679769 150mg od (Day 1 only, placebo subsequently) + ondansetron 8mg bid for 3 days
Group F: GW679769 150mg od + ondansetron 16mg od for 3 days.

Immediately prior to the initiation of chemotherapy, all subjects also received a single IV dose of dexamethasone 8mg.

Objectives: To determine the optimal oral dose of GW679769 when administered in combination with ondansetron hydrochloride and dexamethasone for the prevention of nausea and vomiting during the first 120h in subjects receiving their first cycle of MEC.

Primary Outcome/Efficacy Variable: The proportion of subjects achieving a complete response (no vomiting, no retching, no rescue therapy, and no premature discontinuation from the study) for each treatment arm during the 120h evaluation period following the initiation of MEC. The proportion of subjects experiencing significant nausea during the 120h evaluation period following the initiation of the first cycle of MEC, as assessed by a Visual Analogue Scale (VAS).

Secondary Outcome/Efficacy Variable(s): The proportion of subjects with complete response and significant nausea during the acute (0 to 24h) and delayed (24 to 120h) phase following initiation of MEC. The proportion of subjects with complete protection, total control, nausea, and vomiting during the 120h evaluation period following initiation of MEC. Time to event endpoints (time to emesis, time to first rescue medication). Safety assessments, including routine physical exam findings, vital signs, routine clinical laboratory tests, clinical monitoring and/or observation, and adverse events (AEs) reporting. The impact on daily life activities in subjects during the 120h evaluation period following the initiation of the first cycle of MEC, as assessed by a Functional Living Index – Emesis (FLIE) questionnaire. Population pharmacokinetic/pharmacodynamic parameters, including an assessment of significant covariates.

Statistical Methods: The Intent-to-Treat (ITT) Population was the primary population of interest and was defined as all subjects who were randomized to one of the six treatment regimens (Groups A, B, C, D, E and F). The ITT population was used for the analysis of efficacy data. The per-protocol population (PP) comprised all randomized and treated subjects without a major protocol violation. The safety population comprised all subjects who received any investigational product. Subjects were excluded from this population only if there was documented evidence that no investigational product (either active or placebo) was administered. Efficacy variables included: complete response – no vomiting, no retching, no rescue therapy and no premature discontinuation from the study; complete protection – no vomiting, no retching, no rescue therapy, no premature withdrawal and no significant nausea; total control – no vomiting, no retching, no rescue therapy, no premature withdrawal and no nausea; vomiting – vomited or retched; significant nausea – maximum nausea score $\geq$25mm on the VAS for nausea; nausea – maximum nausea score $\geq$5mm on the VAS for nausea. The primary endpoints, complete response, and significant nausea, were assessed in the first 120h following the start of MEC. All endpoints were assessed as acute (0 to 24h), delayed (24 to 120h), and overall (0 to 120h) following MEC. Testing of dose-response was performed with a two-sided test at the 0.05 significance level. Both of the primary comparisons of interest were required to be significant at the 0.05 significance level.

Study Population: Male and female subjects aged ≥18years with a malignant solid tumor receiving their first course of MEC. Subjects scheduled to receive adjuvant chemotherapy with a cyclophosphamide containing regimen were excluded; however, neo-adjuvant cyclophosphamide containing regimens were allowed.

Number of Subjects:	**Treatment group**					
	A	**B**	**C**	**D**	**E**	**F**
Planned, N	118	118	118	118	118	118
Randomized, N	121	120	121	120	120	121
Completed, n (%)	99 (82)	100 (83)	109 (90)	106 (88)	103 (86)	99 (82)
Total Withdrawn, n (%)	22 (18)	20 (17)	12 (10)	14 (12)	17 (14)	22 (18)
Withdrawn due to Adverse Events, n (%)	4 (3)	4 (3)	3 (2)	2 (2)	4 (3)	7 (6)
Withdrawn due to Lack of Efficacy, n (%)	5 (4)	2 (2)	2 (2)	1 (<1)	0	1 (<1)
Withdrawn for Other Reasons, n (%)	13 (11)	14 (12)	7 (6)	11 (9)	13 (11)	14 (12)
Demographics						
N (ITT)	121	120	121	120	120	121
Females: Males	74: 47	74: 46	72: 49	72: 48	72: 48	72: 49
Mean age, years (SD)	57.0 (11.86)	58.5 (11.77)	57.4 (12.71)	59.2 (12.05)	57.9 (12.95)	57.9 (12.90)
Mean weight, kg (SD)	71.4 (16.34)	71.2 (17.13)	70.6 (17.12)	71.9 (16.49)	70.3 (16.64)	71.8 (15.72)
White, n (%)	90 (74)	94 (78)	80 (66)	95 (79)	78 (65)	93 (77)
Baseline Characteristics						
N (ITT)	121	120	121	120	120	121
FLIE Total Score (Nausea + Vomiting), mean (SD)	121.4 (8.51)	122.8 (7.43)	122.3 (9.07)	122.8 (7.12)	120.0 (11.57)	121.4 (10.13)
Karnofsky Performance Status, n (%)						
100	58 (48)	62 (52)	55 (45)	56 (47)	52 (43)	48 (40)
90	34 (28)	40 (33)	48 (40)	43 (36)	41 (34)	44 (36)
80	22 (18)	15 (13)	16 (13)	18 (15)	23 (19)	22 (18)
70	7 (6)	3 (3)	2 (2)	3 (3)	3 (3)	7 (6)

FLIE = Functional Living Index – Emesis.
Group A = placebo + ondansetron 8mg bid, Group B = GW679769 50mg od + ondansetron 8mg bid, Group C = GW679769 100mg od + ondansetron 8mg bid, Group D = GW679769 150mg od + ondansetron 8mg bid, Group E = GW679769 150mg on Day 1 + ondansetron 8mg bid, Group F = GW679769 150mg od + ondansetron 16mg od.

Primary Efficacy Results:

	Treatment group			
	A	**B**	**C**	**D**
N (ITT)	121	120	121	120
Complete Response (0 to 120h)				
No, n (%)	37 (30.6)	23 (19.2)	26 (21.5)	19 (15.8)
Yes, n (%)	84 (69.4)	97 (80.8)	95 (78.5)	101 (84.2)
Trend test p value	0.0127			
Contrast p value		0.0305	0.0846	0.0127
Significant Nausea (0 to 120h)				
Yes, n (%)	35 (28.9)	33 (27.5)	36 (29.8)	34 (28.3)
No, n (%)	86 (71.1)	87 (72.5)	85 (70.2)	86 (71.7)
Trend test p value	0.9830			

Group A = placebo + ondansetron 8mg bid, Group B = GW679769 50mg od + ondansetron 8mg bid, Group C = GW679769 100mg od + ondansetron 8mg bid, Group D = GW679769 150mg od + ondansetron 8mg bid

Secondary Outcome Variables:				
Efficacy Variables	**Treatment group**			
	A	**B**	**C**	**D**
N (ITT)	121	120	121	120
Complete response				
Acute (0 to 24h)				
No	13 (10.7)	10 (8.3)	13 (10.7)	10 (8.3)
Yes	108 (89.3)	110 (91.7)	108 (89.3)	110 (91.7)
Delayed (24 to 120h)				
No	37 (30.6)	23 (19.2)	26 (21.5)	19 (15.8)
Yes	84 (69.4)	97 (80.8)	95 (78.5)	101 (84.2)
Significant nausea				
Acute (0 to 24h)				
Yes	12 (9.9)	15 (12.5)	17 (14.0)	10 (8.3)
No	109 (90.1)	105 (87.5)	104 (86.0)	110 (91.7)
Delayed (24 to 120h)				
Yes	32 (26.4)	30 (25.0)	31 (25.6)	32 (26.7)
No	89 (73.6)	90 (75.0)	90 (74.4)	88 (73.3)
Complete protection (0 to 120h)				
No	48 (39.7)	40 (33.3)	45 (37.2)	43 (35.8)
Yes	73 (60.3)	80 (66.7)	76 (62.8)	77 (64.2)
Total control (0 to 120h)				
No	61 (50.4)	52 (43.3)	66 (54.5)	56 (46.7)
Yes	60 (49.6)	68 (56.7)	55 (45.5)	64 (53.3)
Vomiting (0 to 120h)				
Yes	28 (23.1)	14 (11.7)	19 (15.7)	13 (10.8)
No	93 (76.9)	106 (88.3)	102 (84.3)	107 (89.2)
Nausea (0 to 120h)				
Yes	55 (45.5)	50 (41.7)	62 (51.2)	52 (43.3)
No	66 (54.5)	70 (58.3)	59 (48.8)	68 (56.7)
Time to emesis				
Subjects with event	28 (23.1)	14 (11.7)	19 (15.7)	13 (10.8)
Censored subjects	93 (76.9)	106 (88.3)	102 (84.3)	107 (89.2)
Time to first rescue medication				
Subjects with event	9 (7.4)	7 (5.8)	4 (3.3)	6 (5.0)
Censored subjects	112 (92.6)	113 (94.2)	117 (96.7)	114 (95.0)
Quality of life: Total (Nausea + Vomiting) FLIE score 0 to 120h	**Treatment group**			
	A	**B**	**C**	**D**
N	113	112	115	111
Mean (SD)	115.2 (18.2)	115.2 (20.9)	113.7 (19.1)	116.4 (16.6)
Median	124.5	125.0	124.1	125.0
Range	41.0 –126.0	20.9 –126.0	36.0 –126.0	36.8–126.0
Group A = placebo + ondansetron 8mg bid, Group B = GW679769 50mg od + ondansetron 8mg bid, Group C = GW679769 100mg od + ondansetron 8mg bid, Group D = GW679769 150mg od + ondansetron 8mg bid				
Pharmacokinetic Results: The pharmacokinetics of GW679769 and GSK525060 were adequately described by linear two-compartment models.				

Safety Results: Adverse events were collected throughout the 5-day assessment period.						
Most Frequent AEs:	**Treatment group**					
	A	**B**	**C**	**D**	**E**	**F**
	N=119	N=119	N=121	N=116	N=117	N=119
Subjects with AEs, n (%)	85 (71)	82 (69)	92 (76)	90 (78)	75 (64)	90 (76)
Most frequent five AEs in each treatment group, n (%)						
Nausea	22 (18)	22 (18)	36 (30)	25 (22)	21 (18)	21 (18)
Anemia	20 (17)	17 (14)	16 (13)	19 (16)	14 (12)	15 (13)
Fatigue	20 (17)	14 (12)	28 (23)	25 (22)	21 (18)	25 (21)
Constipation	16 (13)	16 (13)	15 (12)	14 (12)	18 (15)	17 (14)
Neutropenia	14 (12)	17 (14)	18 (15)	15 (13)	16 (14)	17 (14)
Vomiting	14 (12)	5 (4)	9 (7)	5 (4)	8 (7)	5 (4)
Alopecia	11 (9)	12 (10)	21 (17)	18 (16)	14 (12)	15 (13)
Diarrhea	8 (7)	15 (13)	10 (8)	17 (15)	13 (11)	17 (14)
Anorexia	7 (6)	8 (7)	23 (19)	8 (7)	14 (12)	9 (8)
Serious Adverse Events (SAEs) Includes fatal and non-fatal events	**Treatment group**					
	A	**B**	**C**	**D**	**E**	**F**
	N=119	N=119	N=121	N=116	N=117	N=119
Subjects with any SAE, n (%) [n considered by the investigator to be related to study medication]	11 (9)	10 (8)	16 (13)	17 (15)	9 (8)	15 (13)
Abdominal pain	-	1 (<1) [0]	1 (<1) [0]	-	-	-
Anemia	1 (<1) [0]	1 (<1) [0]	-	2 (2) [0]	1 (<1) [0]	-
Asthenia	-	-	1 (<1) [0]	-	-	1 (<1) [0]
Atrial fibrillation	-	1 (<1) [0]	-	-	1 (<1) [0]	-
Nausea	-	-	2 (2) [0]	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Vomiting	1 (<1) [0]	1 (<1) [0]	-	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Chest pain	-	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]	-	-
Convulsion	2 (2) [0]	1 (<1) [0]	-	-	-	-
Diarrhea	-	1 (<1) [0]	-	1 (<1) [0]	-	1 (<1) [0]
Deep vein thrombosis	-	-	1 (<1) [0]	1 (<1) [0]	-	-
Dehydration	2 (2) [0]	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Dyspnea	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]	2 (2) [0]	-	-
Fatigue	-	-	-	1 (<1) [0]	1 (<1) [1]	-
Febrile neutropenia	-	1 (<1) [0]	-	1 (<1) [0]	1 (<1) [0]	1 (<1) [0]
Gastrointestinal haemorrhage	-	-	-	1 (<1) [0]	-	1 (<1) [0]
Granulocytopenia	-	2 (2) [0]	1 (<1) [0]	-	1 (<1) [0]	-
Hemoptysis	1 (<1) [0]	-	-	-	-	1 (<1) [0]
Hepatic encephalopathy	-	-	-	-	-	1(<1) [1]
Hepatic function abnormal	-	-	-	-	-	2 (2) [1]
Hypersensitivity	-	-	-	-	-	1(<1) [1]
Hyponatremia	-	-	2 (2) [0]	1 (<1) [0]	-	-
Ileus	-	-	1 (<1) [0]	-	-	1 (<1) [1]
Metastases to CNS	2 (2) [0]	-	-	-	-	-
Neutropenia	-	1 (<1) [0]	3 (2) [0]	-	-	1 (<1) [0]
Neutropenic sepsis	1 (<1) [0]	-	-	-	1 (<1) [0]	1 (<1) [0]
Pleuritic pain	-	-	1(<1) [1]	-	-	-
Edema peripheral	-	1 (<1) [0]	-	1 (<1) [0]	-	-
Urinary tract infection	-	-	-	-	-	2 (2) [0]
Abdominal discomfort	-	-	-	-	-	1(<1) [0]
Constipation	-	-	-	-	1(<1) [0]	-
Gastric ulcer perforation	-	-	-	-	1(<1) [0]	-
Gastritis	-	-	-	-	-	1(<1) [0]
Small intestinal obstruction	-	-	1(<1) [0]	-	-	-

Upper gastrointestinal hemorrhage	-	-	1(<1) [0]	-	-	-
Leucopenia	-	-	1(<1) [0]	-	-	-
Lymphopenia	-	-	-	-	-	1(<1) [0]
Thrombocytopenia	-	-	-	-	1(<1) [0]	-
Abdominal abscess	-	-	1(<1) [0]	-	-	-
Candidiasis	-	-	1(<1) [0]	-	-	-
Cellulitis	-	-	-	-	-	1(<1) [0]
Enteritis infectious	-	-	-	-	1(<1) [0]	-
Lung abscess	-	-	-	1(<1) [0]	-	-
Meningitis bacterial	-	-	-	1(<1) [0]	-	-
Pneumonia	-	-	-	1(<1) [0]	-	-
Purulent discharge	-	1(<1) [0]	-	-	-	-
Urethritis	1(<1) [0]	-	-	-	-	-
Cough	-	-	1(<1) [0]	-	-	-
Pulmonary embolism	-	-	-	1(<1) [0]	-	-
Respiratory acidosis	-	1(<1) [0]	-	-	-	-
Respiratory failure	-	1(<1) [0]	-	-	-	-
Drug withdrawal syndrome	-	-	-	-	1(<1) [0]	-
Malaise	-	-	1(<1)[0]	-	-	-
Hypokalemia	-	-	-	1(<1) [0]	-	-
Cardiac failure	-	-	-	-	-	1(<1) [0]
Cardiac failure congestive	-	1(<1) [0]	-	-	-	-
Cardio-respiratory arrest	1(<1) [0]	-	-	-	-	-
Palpitations	-	-	1(<1) [0]	-	-	-
Pericardial effusion	-	-	-	1(<1) [0]	-	-
Myoclonus	1(<1) [0]	-	-	-	-	-
Syncope	1(<1) [0]	-	-	-	-	-
Back pain	-	-	1(<1) [0]	-	-	-
Muscular weakness	-	-	1(<1) [0]	-	-	-
Musculoskeletal chest pain	1(<1) [0]	-	-	-	-	-
Pain in extremity	-	-	-	1(<1) [0]	-	-
Hypotension	-	-	-	1(<1) [0]	-	-
Thrombosis	-	-	-	1(<1) [0]	-	-
Vena cava thrombosis	-	-	-	1(<1) [0]	-	-
Cholelithiasis	-	1(<1) [0]	-	-	-	-
Confusional state	-	-	-	1(<1) [0]	-	-
Mania	-	-	-	1(<1) [0]	-	-
Mental status changes	-	-	-	-	-	1(<1) [0]
Ankle fracture	1(<1) [0]	-	-	-	-	-
Renal failure	-	-	1(<1) [0]	-	-	-
Skin maceration	-	1(<1) [0]	-	-	-	-
Fatal SAEs	**Treatment group**					
	A	**B**	**C**	**D**	**E**	**F**
	N=119	N=119	N=121	N=116	N=117	N=119
Subjects with any fatal SAE, n (%) [n considered by the investigator to be related to study medication]	3 (3)	2 (2)	1 (1)	1 (1)	2 (2)	3 (3)
Granulocytopenia	1(<1) [0]	-	-	-	1(<1) [0]	-
Cardiorespiratory arrest	1(<1) [0]	-	-	-	-	-
Cardiac failure	-	-	-	-	-	1(<1) [0]
Thrombosis	-	-	-	1(<1) [0]	-	-
Hepatic function abnormal	-	-	-	-	-	1(<1) [0]
Neutropenic sepsis	-	-	-	-	1(<1) [0]	-
Back pain	-	-	1(<1) [0]	-	-	-
CNS metastases	1(<1) [0]	-	-	-	-	-

Hemoptysis	1(<1) [0]	-	-	-	-	1(<1) [0]
Respiratory acidosis	-	1(<1) [0]	-	-	-	-
Atrial fibrillation	-	1(<1) [0]	-	-	-	-
Respiratory failure	-	1(<1) [0]	-	-	-	-
Neutropenia	1(<1) [0]	-	-	-	-	-
Adverse events leading to discontinuation	**Treatment group**					
	A	**B**	**C**	**D**	**E**	**F**
	N=119	N=119	N=121	N=116	N=117	N=119
Subjects with AE leading to discontinuation, n (%)	8 (7)	9 (8)	7 (6)	3 (3)	10 (9)	9 (8)
AEs leading to discontinuation in ≥1 subject, n (%)						
Nausea	-	2 (2)	1 (<1)	1 (<1)	-	1 (<1)
Granulocytopenia	-	1 (<1)	-	-	1 (<1)	1 (<1)
Hepatic function abnormal	-	1 (<1)	-	-	-	2 (2)
Rash	-	1 (<1)	-	-	2 (2)	-
Abdominal pain	-	-	1 (<1)	-	1 (<1)	-
Atrial fibrillation	-	1 (<1)	-	-	1 (<1)	-
Convulsion	2 (2)	-	-	-	-	-
Dehydration	1 (<1)	-	-	-	1 (<1)	-
Drug hypersensitivity	1 (<1)	1 (<1)	-	-	-	-
Hemoptysis	1 (<1)	-	-	-	-	1 (<1)
Hypersensitivity	-	1 (<1)	-	-	-	1 (<1)
Ileus	-	-	1 (<1)	-	-	1 (<1)
Leukopenia	-	-	-	-	1 (<1)	1 (<1)
Metastases to CNS	2 (2)	-	-	-	-	-
Thrombocytopenia	-	-	-	-	1 (<1)	1 (<1)
Vomiting	-	-	1 (<1)	-	1 (<1)	-
Group A = placebo + ondansetron 8mg bid, Group B = GW679769 50mg od + ondansetron 8mg bid, Group C = GW679769 100mg od + ondansetron 8mg bid, Group D = GW679769 150mg od + ondansetron 8mg bid, Group E = GW679769 150mg on Day 1 + ondansetron 8mg bid, Group F = GW679769 150mg od + ondansetron 16mg od						
Conclusion: For the primary endpoint of complete response in the first four treatment groups (ITT population), there was a statistically significant monotonic dose response, as indicated by the Cochran-Armitage trend test ($p<0.05$) over 0 to 120h. A statistically significant dose response was not observed for the primary endpoint of significant nausea over 0 to 120h in the ITT population ($p\geq0.05$). Efficacy results suggest that all three active treatment regimens (GW679769 50, 100, and 150mg od for 3 days) were equally clinically effective, indicating that any of these regimens would be suitable for Phase III testing. Across all six treatment arms, the most frequently reported adverse events were nausea, anemia and fatigue.						
Publications: None.						