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.: NKV20001
Title: A Phase II Multicentre, Randomised, Double-Blind, Placebo and Active-Controlled, Dose-Ranging, Parallel Group Study of the Safety and Efficacy of the oral neurokinin-1 receptor antagonist, GW679769 When Administered at daily doses of 50 mg, 100 mg, and 150 mg Oral Tablets in Combination with Ondansetron Hydrochloride and Dexamethasone for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Cancer Subjects Receiving Highly Emetogenic Cisplatin-based Chemotherapy.
Rationale: There remains a significant unmet clinical need in the treatment options available to treat highly emetic chemotherapy (HEC) induced nausea and vomiting (CINV). Standard therapy using a 5-HT_3 antagonist and dexamethasone significantly reduces emesis in the acute (0-24 hour) phase, but that effect does not extend to adequate control of delayed (24-120 hour) phase emesis. Neurokinin-1 receptor antagonists (NK-1 RAs) are thought to exhibit antiemetic activity by suppressing the activity of the nucleus tractus solitarius, which is where the vagal afferents from the gastrointestinal tract converge with inputs from the area postrema and other regions of the brain believed to be important in the control and integration of emesis. NK-1 RAs have previously demonstrated efficacy in preventing cisplatin-induced CINV. This study assessed whether orally administered NK-1 RA GW679769, when given in combination with ondansetron plus dexamethasone improved the control of CINV for 120 h following the administration of cisplatin-based HEC
Phase: II.
Study Period: 08Feb2005 – 09Dec2005.
Study Design: A Phase II, multicentre, randomized, double-blind, placebo and active controlled, parallel group study.
Centres: Forty-seven centres in 18 countries.
Indication: Chemotherapy-induced nausea and vomiting.
Treatment: On Day 1, 1 h prior to chemotherapy, an oral dose of GW679769 (active or placebo) and aprepitant 125 mg (active or placebo) were administered, followed at 30 minutes prior to the initiation of chemotherapy, by an intravenous (IV) dose of ondansetron hydrochloride (HCl), and an oral dose of dexamethasone. Approximately 15 minutes following completion of ondansetron HCl on Day 1, IV cisplatin $\geq$70 mg/m^2 was given. Subjects were randomized to one of six treatment groups as follows: Group 1: GW679769 0 mg on Days 1–3 with dexamethasone 20 mg single dose on Day 1 and dexamethasone 8 mg twice daily (BID) on Days 2–4, and aprepitant placebo Days 1-3. Group 2: GW679769 50 mg on Days 1–3 with dexamethasone 12 mg single dose on Day 1, dexamethasone 8 mg once daily (OD) on Days 2–4 and placebo OD on Days 2–4, and aprepitant placebo Days 1-3. Group 3: GW679769 100 mg on Days 1–3 with dexamethasone 12 mg single dose on Day 1, dexamethasone 8 mg OD on Days 2–4 and placebo OD on Days 2–4, and aprepitant placebo Days 1-3. Group 4: GW679769 150 mg on Days 1–3 with dexamethasone 12 mg single dose on Day 1, dexamethasone 8 mg OD on Days 2–4 and placebo OD on Days 2–4, and aprepitant placebo Days 1-3. Group 5: GW679769 150 mg on Day 1 with dexamethasone 12 mg single dose on Day 1 and dexamethasone 8 mg BID on Days 2–4, and aprepitant placebo Days 1-3. Group 6: Aprepitant 125 mg on Day 1 and 80 mg on Days 2–3, with dexamethasone 12 mg single dose on Day 1, dexamethasone 8 mg OD on Days 2–4 and placebo OD on Days 2–4, and GW679769 placebo Days 1-3. All subjects received (Groups 1-6) received ondansetron HCl 32mg IV on Day 1.
Objectives: To determine the optimal antiemetic dose of oral GW679769 when administered in combination with ondansetron HCl and dexamethasone for the prevention of emesis during the first 120 h following initiation of the first cycle of highly emetogenic cisplatin-based chemotherapy.
Primary Outcome/Efficacy Variable: The proportion of subjects who achieved a complete response (defined as no vomiting, no retching, no rescue therapy, and no premature discontinuation from the study) during the 120-h evaluation period following initiation of highly emetogenic cisplatin-based chemotherapy.
Secondary Outcome/Efficacy Variables: Proportion of subjects with complete response during the acute (0–24 h) and delayed (24–120 h) phase; proportion of subjects with complete protection (no vomiting, no retching, no rescue therapy, no premature withdrawal, maximum nausea <25 on the visual analogue scale [VAS]), total control (no vomiting, no retching, no rescue therapy, no premature withdrawal, maximum nausea VAS <5), and vomiting, during the overall (0–120 h), acute (0–24 h) and delayed (24–120 h) phase; proportion of subjects with significant nausea (maximum nausea VAS $\geq$25) during the acute, delayed, and overall phase, and nausea (maximum nausea VAS $\geq$5) during the acute, delayed, and overall phase; time to emesis, time to rescue; safety assessments; subject satisfaction

questionnaire; and population pharmacokinetic/ pharmacodynamic parameters for GW679769 and its metabolite (GSK525060).

Statistical Methods: For primary (complete response) and secondary efficacy endpoints, the null hypothesis of no dose response was tested against the alternative hypothesis of non-decreasing monotonic response, using the two-sided Cochran-Armitage trend test at the 0.05 significance level. The study was powered at 90% to detect a monotonic dose response and a 25% improvement in the complete response rate in groups 2 to 4 for 120 hours over placebo. The SAS-based procedure Multtest was used to test the null hypothesis. To identify the doses that exhibited a treatment effect, ordinal contrasts were fitted using the Multtest procedure. The primary analysis was stratified by gender.

For proportion endpoints (complete protection, total control, vomiting, significant nausea, nausea) the proportion of subjects who achieved each efficacy endpoint was compared between placebo and each of the active dose groups 2 to 4 as described for the primary endpoint. Time-to-event endpoints (time to first emetic event and first rescue medication) were summarised using Kaplan-Meier analysis.

Groups 5 and 6 were included for exploratory purposes. For all endpoints Group 5 was compared with Group 1 (placebo) and differences in proportions of successes and 95% Confidence Intervals were calculated. Proportions of successes were calculated for Group 6.

Safety and health outcomes endpoints were not formally tested statistically.

Study Population: Male and female (of non-childbearing potential) subjects aged ≥18 years, with a malignant solid tumor for which a first treatment course with a high-dose (≥70 mg/m^2) cisplatin-based regimen was appropriate. Subjects with a Karnofsky Performance score of ≥70, white blood cells >3000/mm^3, platelets >100,000/mm^3, and serum creatinine <1.5 mg/dL.

	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**	**Group 6**	**Total**
Number of Subjects:							
Planned, N	82	82	82	82	82	82	492
Randomised, N	84	82	81	81	83	82	493
Completed, n (%)	66 (79)	65 (79)	72 (89)	65 (80)	65 (78)	64 (78)	397 (81)
Total Withdrawn (any reason), n (%)	18 (21)	17 (21)	9 (11)	16 (20)	18 (22)	18 (22)	96 (19)
Withdrawn due to Adverse Events n (%)	4 (5)	8 (10)	2 (2)	4 (5)	5 (6)	1 (1)	24 (5)
Withdrawn due to Lack of Efficacy n (%)	2 (2)	1 (1)	0	0	0	0	3 (<1)
Withdrawn due to other reasons n (%)	12 (14)	8 (10)	7 (9)	12 (15)	13 (16)	17 (21)	69 (14)

Primary Efficacy Results: A summary of proportion of subjects with complete response 0–120 h (ITT population) is presented in the following table:

	GW679769 + Dexamethasone + Ondansetron			
	Group 1	Group 2	Group 3	Group 4
	0 mg N = 84 n (%)	50 mg N = 82 n (%)	100 mg N = 81 n (%)	150 mg N = 81 n (%)
Complete response	50 (59.5)	62 (75.6)	70 (86.4)	62 (76.5)
Trend test p value	0.0036			
Contrast p value		0.0155	0.0001	0.0036

Secondary Efficacy Results: A summary of proportion based secondary endpoints (ITT Population) is presented in the following table:

	GW679769 + Dexamethasone + Ondansetron			
	Group 1	Group 2	Group 3	Group 4
	0 mg N = 84 n (%)	50 mg N = 82 n (%)	100 mg N = 81 n (%)	150 mg N = 81 n (%)
Complete response				
0-24 h	72 (85.7)	74 (90.2)	78 (96.3)	72 (88.9)
24-120 h	50 (59.5)	62 (75.6)	70 (86.4)	62 (76.5)
Complete protection				
0-120 h	35 (41.7)	41 (50.0)	48 (59.3)	40 (49.4)

0-24 h	63 (75.0)	61 (74.4)	66 (81.5)	57 (70.4)
24-120 h	35/84 (41.7)	41/82 (50.0)	48/81 (59.3)	40/81 (49.4)
Total Control				
0-120 h	27 (32.1)	30 (36.6)	34 (42.0)	32 (39.5)
0-24 h	57 (67.9)	54 (65.9)	52 (64.2)	53 (65.4)
24-120 h	27 (32.1)	30 (36.6)	34 (42.0)	32 (39.5)
No vomiting				
0-120 h	54 (64.3)	64 (78.0)	72 (88.9)	63 (77.8)
0-24 h	75 (89.3)	75 (90.2)	79 (97.5)	73 (90.1)
24-120 h	54 (64.3)	64 (78.0)	72 (88.9)	63 (77.8)
No significant nausea				
0-120 h	45 (53.6)	47 (57.3)	50 (61.7)	45 (55.6)
0-24 h	66 (78.6)	66 (80.5)	66 (81.5)	60 (74.1)
24-120 h	45 (53.6)	47 (57.3)	50 (61.7)	45 (55.6)
No nausea				
0-120 h	33 (39.3)	31 (37.8)	34 (42.0)	34 (42.0)
0-24 h	60 (71.4)	57 (69.5)	52 (64.2)	54 (66.7)
24-120 h	33 (39.3)	31 (37.8)	34 (42.0)	34 (42.0)
Took rescue medication				
0-120 h	7 (8.3)	7 (8.5)	2 (2.5)	3 (3.7)
0-24 h	2 (2.4)	2 (2.4)	0	1 (1.2)
24-120 h	7 (8.3)	7 (8.5)	2 (2.5)	3 (3.7)

A summary of time to event endpoints (ITT population) is presented in the following table:

	GW679769 + Dexamethasone + Ondansetron			
	Group 1	Group 2	Group 3	Group 4
	0 mg N = 84 n (%)	50 mg N = 82 n (%)	100 mg N = 81 n (%)	150 mg N = 81 n%)
Time to emesis				
Subjects with event	30 (35.7)	18 (22.0)	9 (11.1)	18 (22.2)
Censored subjects	54 (64.3)	64 (78.0)	72 (88.9)	63 (77.8)
Time to rescue				
Subjects with event	7 (8.3)	7 (8.5)	2 (2.5)	3 (3.7)
Censored subjects	77 991.7)	75 (91.5)	79 (97.5)	78 (96.3)

A summary of secondary efficacy endpoints–exploratory analyses (ITT population) is presented in the following table:

	GW679769 + Dexamethasone + Ondansetron			Aprepitant[2]
	Group 1	Group 5	Difference[1]	Group 6
	0 mg N = 84 n (%)	150 mg Day 1 N = 83 n (%)	(95% confidence interval) (%)	125 mg/80 mg N = 82 n (%)
Complete Response				
0–120 h	50 (59.5)	62 (74.7)	15.2 (1.1, 29.2)	59 (72.0)
0–24 h	72 (85.7)	77 (92.8)	7.1 (-2.3, 16.4)	74 (90.2)
24–120 h	50 (59.5)	62 (74.7)	15.2 (1.1, 29.2)	59 (72.0)
Complete protection				
0–120 h	35 (41.7)	39 (47.0)	5.3 (-9.7, 20.4)	40 (48.8)
0–24 h	63 (75.0)	66 (79.5)	4.5 (-8.2, 17.2)	56 (68.3)
24–120 h	35 (41.7)	39 (47.0)	5.3 (-9.7, 20.4)	40 (48.8)
Total control				
0–120 h	27 (32.1)	33 (39.8)	7.6 (-6.9, 22.1)	29 (35.4)
0–24 h	57 (67.9)	58 (69.9)	2.0 (-12.0, 16.1)	47 (57.3)
24–120 h	27 (32.1)	33 (39.8)	7.6 (-6.9, 22.1)	29 (35.4)
No vomiting				
0–120 h	54 (64.3)	65 (78.3)	-14.0 (-27.6, -0.5)	65 (79.3)

0–24 h	75 (89.3)	80 (96.4)	-7.1 (-14.8, 0.6)	76 (92.7)
24–120 h	54 (64.3)	65 (78.3)	-14.0 (-27.6, -0.5)	65 (79.3)
No significant nausea				
0–120 h	45 (53.6)	46 (55.4)	-1.9 (-17.0, 13.3)	44 (53.7)
0–24 h	66 (78.6)	70 (84.3)	-5.8 (-17.5, 6.0)	60 (73.2)
24–120 h	45 (53.6)	46 (55.4)	-1.9 (-17.0, 13.3)	44 (53.7)
No nausea				
0–120 h	33 (39.3)	35 (42.2)	-2.9 (-17.8. 12.0)	30 (36.6)
0–24 h	60 (71.4)	60 (72.3)	-0.9 (-14.5, 12.8)	48 (58.5)
24–120 h	33 (39.3)	35 (42.2)	-2.9 (-17.8. 12.0)	30 (36.6)
Rescue				
0–120 h	7 (8.3)	5 (6.0)	-2.3 (-10.1, 5.5)	7 (8.5)
0–24 h	2 (2.4)	2 (2.4)	0.0 (-4.6, 4.7)	1 (1.2)
24–120 h	7 (8.3)	5 (6.0)	-2.3 (-10.1, 5.5)	7 (8.5)

1. Group 5 – Group 1
2. Plus dexamethasone (dex) + ondansetron

Pharmacokinetic Results: The pharmacokinetics of GW679769 and GSK525060 were adequately described by linear two-compartment models.

Health Outcomes Results: A summary of subject satisfaction from 0 – 120 h (ITT population) is presented in the following table:

	GW679769 + Dexamethasone + Ondansetron					Aprepitant[1]
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
	0 mg N = 84 n (%)	50 mg N = 82 n (%)	100 mg N = 81 n (%)	150 mg N = 81 n (%)	150 mg D1 N = 83 n (%)	125/80 mg N = 82 n (%)
Very satisfied	37 (44)	39 (48)	46 (57)	50 (62)	42 (51)	38 (46)
Somewhat satisfied	27 (32)	28 (34)	26 (32)	26 (32)	25 (30)	25 (30)
Neither satisfied or dissatisfied	8 (10)	11 (13)	7 (9)	3 (4)	9 (11)	10 (12)
Somewhat dissatisfied	4 (5)	1 (1)	0	1 (1)	5 (6)	3 (4)
Very dissatisfied	4 (5)	0	1 (1)	1 (1)	1 (1)	0

D1 = Day 1 only

1. Plus dexamethasone (dex) + ondansetron

Safety Results: Adverse events were recorded pre-cisplatin and post-dose on Day 1. For Cycle 1, AE questioning was performed as part of the telephone follow-up on study Days 2, 3, 4, and 5 (when possible) as well as at the study site at each return visit. For subsequent cycles, AEs were assessed on Day 1, Day 6–10 (by telephone contact if the subject had been discharged), and at the Day 20–30 visit.

Most Frequent Adverse Events-On-Therapy

	GW679769 + Dexamethasone + Ondansetron					Aprepitant[1]
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
	0 mg N = 83 n (%)	50 mg N = 82 n (%)	100 mg N = 80 n (%)	150 mg N = 81 n (%)	150 mg D1 N = 82 n (%)	125/80 mg N = 80 n (%)
Subjects with any AE	56 (67)	55 (67)	57 (71)	57 (70)	58 (71)	57 (71)
Nausea	17 (20)	16 (20)	13 (16)	9 (11)	16 (20)	12 (15)
Neutropenia	17 (20)	15 (18)	14 (18)	11 (14)	10 (12)	11 (14)
Constipation	9 (11)	7 (9)	10 (13)	7 (9)	11 (13)	7 (9)
Leukopenia	9 (11)	7 (9)	10 (13)	6 (7)	6 (7)	4 (5)
Vomiting	9 (11)	6 (7)	4 (5)	5 (6)	8 (10)	10 (13)
Headache	5 (6)	10 (12)	4 (5)	1 (1)	6 (7)	5 (6)
Anorexia	5 (6)	8 (10)	6 (8)	5 (6)	6 (7)	4 (5)
Hiccups	6 (7)	7 (9)	7 (9)	9 (11)	14 (17)	10 (13)
Asthenia	5 (6)	7 (9)	16 (20)	3 (4)	12 (15)	10 (13)

1. Plus dexamethasone (dex) + ondansetron

Subject with any SAEs, n (%) [n considered by the investigator to be related to study medication] – includes both fatal and non-fatal events

	GW679769 + Dexamethasone + Ondansetron	Aprepitant[1]

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
	0 mg N = 83 n (%)	50 mg N = 82 n (%)	100 mg N = 80 n (%)	150 mg N = 81 n (%)	150 mg D1 N = 82 n (%)	125/80 mg N = 80 n (%)
Subjects with any SAE	8 (10) [0]	8 (10) [0]	8 (10) [0]	11 (14) [0]	13 (16) [1]	11 (14) [0]
Abdominal pain	0	0	0	1 (1) [0]	0	1 (1) [0]
Cardiopulmonary failure	2 (2) [0]	0	0	0	0	0
Fatigue	0	0	1 (1) [0]	0	1 (1) [0]	0
Febrile neutropenia	2 (2) [0]	1 (1) [0]	0	2 (2) [0]	1 (1) [0]	1 (1) [0]
Hiccups	0	0	0	0	1 (1) [1]	1 (1) [0]
Hyponatraemia	0	0	0	1 (1) [0]	0	1 (1) [0]
Infection	0	0	1 (1) [0]	0	1 (1) [0]	0
Leukopenia	0	1 (1) [0]	0	0	1 (1) [0]	0
Mucosal inflammation	0	0	1 (1) [0]	1 (1) [0]	0	0
Neutropenia	1 (1) [0]	1 (1) [0]	1 (1) [0]	0	0	1 (1) [0]
Non-small cell lung cancer	1 (1) [0]*	0	0	0	2 (2) [0]	0
Pneumonia	1 (1) [0]	1 (1) [0]	1 (1) [0]	1 (1) [0]	2 (2) [0]	1 (1) [0]
Pyrexia	0	0	0	1 (1) [0]	1 (1 [0]	0
Renal failure	1 (1) [0]	0	0	1 (1) [0]	1 (1) [0]	0
Sepsis	0	0	1 (1) [0]	0	1 (1) [0]	0
Syncope	0	0	0	1 (1) [0]	0	1 (1) [0]
Fracture	1 (1) [0]*	0	0	0	0	0
Pulmonary embolism	1 (1) [0]	0	0	0	0	0
Superior vena caval occlusion	1 (1) [0]	0	0	0	0	0
Acute pancreatitis	0	1 (1) [0]	0	0	0	0
Arrhythmia	0	1 (1) [0]	0	0	0	0
Asthenia	0	1 (1) [0]	0	0	0	0
Exacerbated dyspnoea	0	1 (1) [0]	0	0	0	0
Hypersensitivity	0	1 (1) [0]	0	0	0	0
Nausea	0	1 (1) [0]	0	0	0	0
Pain	0	1 (1) [0]	0	0	0	0
Diarrhoea	0	0	1 (1) [0]	0	0	0
Dyspnoea	0	0	1 (1) [0]	0	0	0
Hyperglycaemia	0	0	1 (1) [0]	0	0	0
Tumor haemorrhage	0	0	1 (1) [0]	0	0	0
Appendicitis	0	0	0	1 (1) [0]	0	0
Cardio-respiratory arrest	0	0	0	1 (1) [0]	0	0
Neoplasm	0	0	0	1 (1) [0]	0	0
Small-cell lung cancer stage unspecified	0	0	0	1 (1) [0]	0	0
Upper gastroinstinal haemorrhage	0	0	0	1 (1) [0]	0	0
Constipation	0	0	0	0	1 (1) [0]	0
Femur fracture	0	0	0	0	1 (1) [0]	0
Myocardial infarction	0	0	0	0	1 (1) [0]	0
Pathological fracture	0	0	0	0	1 (1) [0]	0
Peripheral ischemia	0	0	0	0	1 (1) [0]	0
Thrombocytopenia	0	0	0	0	1 (1) [0]	0
Anaemia	0	0	0	0	0	1 (1) [0]
Black hairy tounge	0	0	0	0	0	1 (1) [0]**
Dyspepsia	0	0	0	0	0	1 (1) [0]
Epilepsy	0	0	0	0	0	1 (1) [0]
Limb arterial thrombosis	0	0	0	0	0	1 (1) [0]
Pericarditis	0	0	0	0	0	1 (1) [0]

Tounge Disorder	0	0	0	0	0	1 (1) [0]**
Vomiting	0	0	0	0	0	1 (1) [0]

1. Plus dexamethasone (dex) + ondansetron
* Represents single SAE in same subject of "fracture due to progression of non-small cell lung cancer"
** Single SAE in same subject coded twice

Subject with fatal SAEs, n (%) [n considered by the investigator to be related to study medication]

	GW679769 + Dexamethasone + Ondansetron					Aprepitant[1]
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
	0 mg N = 83 n (%)	50 mg N = 82 n (%)	100 mg N = 80 n (%)	150 mg N = 81 n (%)	150 mg D1 N = 82 n (%)	125/80 mg N = 80 n (%)
Cardiopulmonary failure	2 (2) [0]#	0	0	0	0	0
Pulmonary embolism	1 (1) [0]	0	0	0	0	0
Pneumonia	1 (1) [0]#	0	0	0	0	0
Arrhythmia	0	1 (1) [0]	0	0	0	0
Febrile neutropenia	0	1 (1) [0]	0	0	0	0
Dysponea	0	1 (1) [0]	0	0	0	0
Neutropenia	0	0	1 (1) [0]*	0	0	0
Sepsis	0	0	1 (1) [0]*	0	0	0
Small cell lung cancer	0	0	0	1 (1) [0]	0	0
Upper gastrointestinal haemorrhage	0	0	0	1 (1) [0]	0	0
Cardio-respiratory arrest	0	0	0	1 (1) [0]	0	0
Neoplasm	0	0	0	1 (1) [0]	0	0
Non-small cell lung cancer	0	0	0	0	2 (2) [0]^	0
Pneumonia	0	0	0	0	2 (2) [0]^	0
Renal failure	0	0	0	0	1 (1) [0]	0

1. Plus dexamethasone (dex) + ondansetron
* Same subject; # Same subject; ^ One subject had NSCLC and pneumonia events

Conclusion: For the primary endpoint of complete response in the first four treatment groups (ITT population), there was a statistically significant monotonic dose response over 0–120 hours. In general, the absorption of GW679769 was rapid and the pharmacokinetics of GW679769 and GSK525060 were adequately described by linear two-compartment models. The incidence of adverse events was similar across treatment groups; the most commonly reported adverse event was nausea. ·There were no notable differences among treatment groups with regard to subject satisfaction results.

Publications: None.