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: NKV102549
Title: A Phase III, Multicentre, Randomised, Double-Blind, Active Controlled, Parallel Group Study of the Safety and Efficacy of the Intravenous and Oral Formulations of the Neurokinin-1 Receptor Antagonist, Casopitant (GW679769) in Combination with Ondansetron and Dexamethasone for the Prevention of Nausea and Vomiting Induced Moderately Emetogenic Chemotherapy**.**
Rationale: Previous studies support the use of NK-1 receptor antagonists in combination therapy to enhance control of chemotherapy induced nausea and vomiting (CINV) across both acute and delayed phases in the clinical setting. This Phase III study assessed whether the administration of casopitant (intravenous [IV] or oral) in combination with standard 2-drug antiemetic therapy improves the control of CINV over the 120 hours following administration of anthracycline/cyclophosphamide (AC) moderately emetogenic chemotherapy (MEC) regimens.
Phase: III
Study Period: The study start date (first subject first visit) was 20 July 2006 and the completion date for the treatment phase of the study (last subject last visit) was 1 October 2007. The follow-up phase of the study was completed on 28 October 2009. .
Study Design: Randomised, double-blind, active-controlled, 4-arm, parallel-group.
Centres: 196 centres in 32 countries: 84 centres in Europe, 73 in North America, and 39 in International.
Indication: CINV
Treatment: Subjects were randomised to 1 of 4 treatment groups (Control, Single-Dose Oral, 3-Day Oral, 3-Day IV/Oral). All 4 treatment groups received a standard regimen of ondansetron 8 mg oral twice daily on Day 1-3 and dexamethasone 8 mg IV on Day 1. Casopitant was dosed as follows: Control, casopitant placebo on Day 1-3, Single Dose Oral, casopitant 150 mg on Day 1; 3-Day Oral: casopitant 150 mg oral on Day 1 and 50 mg oral on Day 2-3; 3-Day IV/Oral: casopitant 90 mg IV on Day 1 and 50 mg oral on Day 2-3.
Objectives: To assess the efficacy of triple therapy, casopitant, ondansetron and dexamethasone, versus dual therapy, ondansetron and dexamethasone in the prevention of emesis over the first 120 hours following the initiation of the first cycle of an anthracycline and cyclophosphamide containing moderately emetogenic chemotherapy (MEC) regimen.
Primary Outcome/Efficacy Variable: Complete response, defined as no vomiting/retching, and no rescue therapy over the first 120 hours following the initiation the first cycle of MEC.
Secondary Outcome/Efficacy Variable(s): Secondary efficacy endpoints for Cycle 1 included: complete response in the acute (0-24 hours) and delayed (24-120 hours) phases; vomiting, nausea (by a Visual Analogue Scale or a categorical scale), complete protection (complete responders who had no significant nausea) and total control (complete responders who had no nausea) in the overall (0-120 hours), acute and delayed phases; rescue medication use; time to first emetic event/rescue medication use; health outcomes measures. Efficacy in subsequent cycles was assessed by complete response (0-120 hours) in Cycles 2-4. Safety and tolerability were assessed in all Cycles.
Statistical Methods: Assuming a 50% complete response rate for the control group at 120 hours, 460 subjects per group would be required to test a 12% absolute difference between the control group and any of the casopitant treatment groups with 90% power and a 2-sided level of significance of 0.0167 (adjusted for 3 multiple comparisons). The primary efficacy analysis compared control with the casopitant groups for the proportion of subjects achieving complete response 0–120 hours in the modified intent-to treat (MITT) population (randomised subjects who received any investigational product and had MEC administered). The ITT (randomised subjects) was a supportive efficacy population. The Cochran-Mantel-Haenszel test, which adjusts for the stratification factor (gender) was used. P-values, odds ratios and 95% confidence intervals (CI) were reported. If the primary endpoint result was significant ($p<0.0167$) for a particular treatment comparison, then the secondary endpoints of complete response (acute phase) then complete response (delayed phase) were tested hierarchically at the 1.67% level of significance and 98.33% CI were presented. Testing stopped when a hypothesis failed to meet significance. The safety population comprised all randomised subjects who received any investigational product.

Study Population: Chemotherapy naïve, male and female (of non-childbearing potential) subjects aged ≥18 years, scheduled to receive their first course of chemotherapy treatment for a malignant solid tumour with AC-MEC.				
Number of Subjects:	**Control**	**Single-Dose Oral**	**3-Day Oral**	**3-Day IV/Oral**
Planned, N	460	460	460	460
Randomised (ITT), N	483	483	483	484
Completed all Planned Chemotherapy, n (%)	361 (75)	365 (76)	372 (77)	364 (75)
Total Number Subjects Withdrawn, N (%)	122 (25)	118 (24)	111 (23)	120 (25)
Withdrawn due to Adverse Events n (%)	16 (3)	14 (3)	15 (3)	22 (5)
Withdrawn due to Lack of Efficacy n (%)	24 (5)	25 (5)	19 (4)	13 (3)
Withdrawn for Other Reasons n (%)	82 (17)	79 (16)	77 (16)	85 (18)
Demographics	**Control**	**Single-Dose Oral**	**3-Day Oral**	**3-Day IV/Oral**
N (ITT)	483	483	483	484
Females: Males	471: 12	471: 12	472: 11	472: 12
Mean Age, years (SD)	52.6 (10.53)	51.6 (10.63)	51.4 (11.03)	52.5 (11.12)
White, n (%)	355 (74)	345 (73)	332 (70)	338 (71)
Primary Efficacy Results:				
	Control	**Single-Dose Oral**	**3-Day Oral**	**3-Day IV/Oral**
N (MITT)	479	479	480	479
Complete Response 0-120 h, n (%)	284 (59)	351 (73)	350 (73)	353 (74)
Cochran-Mantel-Haenszel Test p-value		<0.0001	<0.0001	<0.0001
Odds Ratio		1.88	1.85	1.92
98.33% CI		1.35, 2.63	1.32, 2.57	1.38, 2.69
Secondary Outcome Variable(s):				
	Control	**Single-Dose Oral**	**3-Day Oral**	**3-Day IV/Oral**
N (MITT)	479	479	480	479
Complete Response 0-24 h, n (%)	406 (85)	421 (88)	427 (89)	412 (86)
Odds Ratio		1.31	1.45	1.11
98.33% CI		0.83, 2.05	0.91, 2.30	0.71, 1.72
Complete Response 24-48 h, n (%)	284 (59)	351 (73)	350 (73)	353 (74)
Odds Ratio		1.88	1.85	1.92
98.33% CI		1.35, 2.63	1.32, 2.57	1.38, 2.69
Vomiting 0-120 h, n (%)	175 (37)	98 (20)	93 (19)	106 (22)
Odds Ratio		0.45	0.42	0.49
98.33% CI		0.31, 0.64	0.29, 0.60	0.35, 0.70
Vomiting 0-24 h, n (%)	65 (14)	45 (9)	41 (9)	59 (12)
Odds Ratio		0.66	0.59	0.89
98.33% CI		0.40, 1.08	0.36, 0.99	0.56, 1.42
Vomiting 24-120 h, n (%)	175 (37)	98 (20)	93 (19)	106 (22)
Odds Ratio		0.45	0.42	0.49
98.33% CI		0.31, 0.64	0.29, 0.60	0.35, 0.70
Maximum Nausea Score (VAS) 0-120 hrs	N=474	N=477	N=476	N=466
Mean (SD)	30.9 (34.7)	27.7 (32.2)	29.2 (33.1)	25.1 (30.7)
Median (Min-Max)	14.5 (0-100)	12.0 (0-100)	13.0 (0-100)	9.0 (0-100)
Maximum Nausea Score (VAS) 0-24 hrs	N=398	N=404	N=385	N=399
Mean (SD)	13.9 (26.6)	16.3 (27.4)	17.0 (27.4)	14.9 (26.2)
Median (Min-Max)	1.0 (0-100)	2.0 (0-100)	2.0 (0-100)	2.0 (0-100)
Maximum Nausea Score (VAS) 24-120 hrs	N=472	N=476	N=474	N=465
Mean (SD)	28.5 (33.1)	24.2 (29.5)	26.4 (31.4)	22.3 (29.0)
Median (Min-Max)	12.0 (0-100)	10.0 (0-100)	12.0 (0-100)	7.0 (0-100)

	Control	Single-Dose Oral	3-Day Oral	3-Day IV/Oral
Significant Nausea (VAS) 0-120 h, n (%)	203 (42)	191 (40)	199 (41)	187 (39)
Odds Ratio		0.90	0.96	0.87
98.33% CI		0.66, 1.23	0.70, 1.32	0.63, 1.19
Significant Nausea (VAS) 0-24 h, n (%)	74 (15)	90 (19)	96 (20)	93 (19)
Odds Ratio		1.27	1.37	1.32
98.33% CI		0.84, 1.91	0.91, 2.06	0.88, 1.99
Significant Nausea (VAS) 24-120 h, n (%)	203 (42)	191 (40)	199 (41)	187 (39)
Odds Ratio		0.90	0.96	0.87
98.33% CI		0.66, 1.23	0.70, 1.32	0.63, 1.19
Nausea (VAS) 0-120 h, n (%)	309 (65)	296 (62)	321 (67)	294 (61)
Odds Ratio		0.89	1.11	0.87
98.33% CI		0.64, 1.23	0.80, 1.54	0.63, 1.20
Nausea (VAS) 0-24 h, n (%)	137 (29)	162 (34)	175 (36)	159 (33)
Odds Ratio		1.28	1.43	1.24
98.33% CI		0.91, 1.78	1.03, 2.00	0.89, 1.74
Nausea (VAS) 24-120 h, n (%)	309 (65)	296 (62)	321 (67)	294 (61)
Odds Ratio		0.89	1.11	0.87
98.33% CI		0.64, 1.23	0.80, 1.54	0.63, 1.20
Maximum Nausea Severity (Categorical Scale) 1-120 h, n (%)				
None	155 (32)	164 (34)	144 (30)	167 (35)
Mild	130 (27)	141 (29)	148 (31)	143 (30)
Moderate	84 (18)	110 (23)	109 (23)	96 (20)
Severe	110 (23)	64 (13)	79 (16)	73 (15)
Maximum Nausea Severity (Categorical Scale) 0-24 h, n (%)				
None	327 (68)	312 (65)	299 (62)	301 (63)
Mild	91 (19)	99 (21)	98 (20)	97 (20)
Moderate	23 (5)	43 (9)	53 (11)	41 (9)
Severe	38 (8)	25 (5)	30 (6)	40 (8)
Maximum Nausea Severity (Categorical Scale) 24-120 h, n (%)				
None	155 (32)	164 (34)	144 (30)	167 (35)
Mild	130 (27)	141 (29)	148 (31)	143 (30)
Moderate	84 (18)	110 (23)	109 (23)	96 (20)
Severe	110 (23)	64 (13)	79 (16)	73 (15)
Complete Protection 0-120 h, n (%)	241 (50)	259 (54)	248 (52)	272 (57)
Odds Ratio		1.16	1.05	1.30
98.33% CI		0.85, 1.59	0.77, 1.43	0.95, 1.77
Complete Protection 0-24 h, n (%)	377 (79)	371 (77)	359 (75)	365 (76)
Odds Ratio		0.93	0.80	0.87
98.33% CI		0.64, 1.35	0.56, 1.16	0.60, 1.26
Complete Protection 24-120 h, n (%)	241 (50)	259 (54)	248 (52)	272 (57)
Odds Ratio		1.16	1.05	1.30
98.33% CI		0.85, 1.59	0.77, 1.43	0.95, 1.77
Total Control 0-120 h, n (%)	158 (33)	178 (37)	152 (32)	184 (38)
Odds Ratio		1.20	0.94	1.27
98.33% CI		0.87, 1.66	0.67, 1.31	0.92, 1.75
Total Control 0-24 h, n (%)	320 (67)	305 (64)	292 (61)	304 (63)
Odds Ratio		0.87	0.77	0.86
98.33% CI		0.63, 1.21	0.56, 1.07	0.62, 1.19

	Control	Single-Dose Oral	3-Day Oral	3-Day IV/Oral
Total Control 24-120 h, n (%)	158 (33)	178 (37)	152 (32)	184 (38)
Odds Ratio		1.20	0.94	1.27
98.33% CI		0.87, 1.66	0.67, 1.31	0.92, 1.75
Complete Response 0-120 h in Cycle 2, n (%)	236 (63)	307 (80)	304 (80)	308 (81)
Complete Response 0-120 h in Cycle 3, n (%)	222 (67)	274 (79)	270 (78)	276 (80)
Complete Response 0-120 h in Cycle 4, n (%)	200 (69)	250 (82)	253 (83)	254 (84)
Rescue Medication Use 0-120 hrs, n (%)	65 (14)	53 (11)	57 (12)	49 (10)
Odds Ratio		0.79	0.86	0.72
98.33% CI		0.49, 1.27	0.54, 1.37	0.45, 1.17
Rescue Medication Use 0-24 hrs, n (%)	18 (4)	20 (4)	18 (4)	18 (4)
Odds Ratio		1.12	1.00	1.00
98.33% CI		0.50, 2.47	0.44, 2.25	0.44, 2.26
Rescue Medication Use 24-120 hrs, n (%)	65 (14)	53 (11)	57 (12)	49 (10)
Odds Ratio		0.79	0.86	0.72
98.33% CI		0.49, 1.27	0.54, 1.37	0.45, 1.17
FLIE Scores 0-120 h				
Total FLIE	N=460	N=462	N=458	N=452
Mean (SD)	103.4 (28.2)	109.1 (20.3)	108.6 (21.7)	110.2 (20.9)
Nausea Subscore	N=462	N=466	N=464	N=455
Mean (SD)	49.3 (15.9)	50.7 (14.0)	49.9 (15.0)	51.8 (13.7)
Vomiting Subscore	N=460	N=463	N=458	N=452
Mean (SD)	54.1 (14.2)	58.3 (9.0)	58.6 (9.7)	58.2 (9.7)
Subject Satisfaction 0-120h, n (%)				
Very Satisfied	256 (53)	270 (56)	271 (56)	282 (59)
Somewhat Satisfied	99 (21)	102 (21)	107 (22)	96 (20)
Neither Satisfied or Dissatisfied	50 (10)	52 (11)	53 (11)	55 (11)
Somewhat Dissatisfied	34 (7)	20 (4)	19 (4)	9 (2)
Very Dissatisfied	22 (5)	22 (5)	13 (3)	11 (2)
Missing	0	2 (<1)	2 (<1)	2 (<1)
Subject Willingness 0-120 h, n (%)				
Definitely Would be Willing	305 (64)	314 (66)	311 (65)	307 (64)
Probably Would be Willing	83 (17)	71 (15)	98 (20)	90 (19)
Not Certain	45 (9)	51 (11)	37 (8)	41 (9)
Probably Would Not be Willing	11 (2)	10 (2)	6 (1)	8 (2)
Definitely Would Not be Willing	16 (3)	21 (4)	10 (2)	5 (1)
Missing	1 (<1)	1 (<1)	3 (<1)	4 (<1)
Safety Results: An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 28 days after the last dose of medication.				
	Control	**Single-Dose Oral**	**3-Day Oral**	**3-Day IV/Oral**
Most Frequent Adverse Events – On-Therapy				
N (Safety)	479	481	481	479
Subjects with any AE(s), n (%)	404 (84)	412 (86)	420 (87)	411 (86)
Neutropenia	201 (42)	214 (44)	230 (48)	202 (42)
Alopecia	156 (33)	169 (35)	149 (31)	154 (32)
Fatigue	113 (24)	135 (28)	124 (26)	116 (24)
Leukopenia	108 (23)	92 (19)	106 (22)	102 (21)
Constipation	100 (21)	89 (19)	84 (17)	92 (19)

Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**				
	Control	**Single-Dose Oral**	**3-Day Oral**	**3-Day IV/Oral**
N (Safety)	479	481	481	479
Subjects with any SAE[1], n (%) [related] **- Includes both fatal and non-fatal events**	29 (6)	25 (5)	31 (6)	27 (6)
Febrile neutropenia	7 (1)	10 (2)	9 (2)	10 (2) [1]
Neutropenia	4 (<1)	5 (1)	3 (<1)	2 (<1)
Vomiting	5 (1) [1]	2 (<1)	2 (<1) [1]	1 (<1)
Nausea	2 (<1)	2 (<1)	3 (<1) [1]	1 (<1)
Anaemia	2 (<1)	1 (<1)	1 (<1)	2 (<1)
Pyrexia	3 (<1)	1 (<1)	0	1 (<1)
Leukopenia	0	2 (<1)	2 (<1)	0
Sepsis	1 (<1)	0	0	2 (<1)
Urinary tract infection	1 (<1)	1 (<1)	0	1 (<1)
Back pain	0	0	2 (<1)	0
Cellulitis[2]	0	0	2 (<1)	0
Chest pain	2 (<1)	0	0	0
Dehydration	1 (<1)	0	1 (<1) [1]	0
Hypotension	1 (<1)	0	0	1 (<1)
Neutropenic sepsis	0	0	2 (<1)	0
Pharyngitis	0	0	2 (<1) [1]	0
Pneumonia	1 (<1)	1 (<1)	0	0
Pulmonary embolism	0	0	1 (<1)	1 (<1)
Syncope	0	0	2 (<1)	0
1. Only SAEs that were reported in more than 1 subject overall are listed here. An additional 9, 10, 11 and 13 SAEs (fatal and non-fatal) were reported in 1 subject only in the Control, Single-Dose Oral, 3-Day Oral and 3-Day IV/Oral groups, respectively. Of these, acute pancreatitis, peripheral ischaemia, hepatic enzyme increased and hyperbilirubinaemia in the Single-Dose Oral Group; fatigue, headache and dyspepsia in the 3-Day Oral group; and chills, dizziness, dyspnoea and tachycardia in the 3-Day IV/Oral group were considered related 2. Combined preferred terms of 'cellulitis' and 'breast cellulitis'				
	Control	**Single-Dose Oral**	**3-Day Oral**	**3-Day IV/Oral**
N (Safety)	479	481	481	479
Subjects with Fatal SAEs, n (%)	1 (<1)	1 (<1)	0[1]	1 (<1)
Renal failure	1 (<1)	0	0	0
Acute myocardial infarction	0	1 (1)	0	0
Sepsis	0	0	0	1 (<1)[2]
Paralytic ileus	0	0	0	1 (<1)[2]
1. One subject in the 3-Day Oral group died due to 'disease under study', and this was not reported as a fatal SAE as per protocol 2. Events in the same subject				

Conclusion:
All casopitant regimens (Single-Dose Oral, 3-Day Oral, 3-Day IV/Oral) were more effective than control (ondansetron and dexamethasone), in preventing CINV in subjects receiving AC-MEC, and demonstrated a clinically acceptable safety profile.

Results from the follow-up Phase: Three patients with troponin values above the 3XULN of 0.12ng/mL entered the follow-up phase and were assessed for cardiac safety at 3, 9 and 24 months. There were no adverse or serious adverse events reported during the follow-up phase. All follow up cardiac assessments were either normal or not changed significantly. The results from the follow-up phase do not alter the safety conclusions of the study.

Publications: None