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Study No.:NKV102551

Title: A Phase III multicentre, randomised, double-blind, active-controlled, parallel group study of the efficacy and safety of the intravenous and oral formulations of the neurokinin-1 receptor antagonist, casopitant (GW679769), administered in combination with ZOFRAN and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in cancer subjects receiving highly emetogenic cisplatin-based 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 cisplatin-based highly emetogenic chemotherapy (HEC) regimens.

Phase: III

Study Period: The study start date (first subject first visit) was 06 November 2006 and the completion date for the treatment phase of the study (last subject last visit) was 09 October 2007.

Study Design: Randomised, double-blind, active-controlled, 3-arm, parallel-group.

Centres: 77 centres in 22 countries: 31 centres in Eastern Europe; 21 in Western Europe, 21 in Asia and 4 in Argentina.

Indication: CINV

Treatment: Subjects were randomised to 1 of 3 treatment groups (Control, Single-Dose Oral, 3-Day IV/Oral). All 3 treatment groups received a standard regimen of ondansetron 32 mg IV once daily on Day 1 and dexamethasone 12 mg or 20 mg oral on Day 1 followed by 8 mg oral once daily Day 2-4. Casopitant was dosed as follows: Control, casopitant placebo on Day 1-3, Single Dose Oral, casopitant 150 mg on Day 1; 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 dexamathasone in the prevention of emesis over the first 120 hours following the initiation of the first cycle of a cisplatin-based highly emetogenic chemotherapy (HEC) 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 HEC.

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, a total of 270 subjects per treatment group was required to show a 15% absolute difference between the Control group and either of the two casopitant treatment groups with 90% power and a two-sided level of significance of 0.025 (adjusted for two primary comparisons to maintain an overall 5% Type I error rate). The primary efficacy analysis compared control (ondansetron and dexamethasone) with the casopitant groups for the proportion of subjects achieving complete response 0–120 hours in the MITT population (randomised subjects who received any investigational product and had HEC administered). The ITT (randomised subjects was a supportive efficacy population. Testing was conducted at the 2.5% level of significance. The Cochran-Mantel-Haenszel test which adjusts for the stratification factors (gender and Hesketh chemotherapy emetogenicity classification score of $\geq$3 or $\leq$2) was used. P values, odds ratios and 95% confidence intervals (CIs) were reported. If the primary endpoint result was significant ($p<0.025$) for a particular treatment comparison, then the secondary endpoints of complete response (acute phase) then complete response (delayed phase) were tested hierarchically at the 2.5% level of significance and 97.5% CI were presented for that treatment comparison. Testing stopped when a hypothesis failed to meet significance. The safety population comprised all randomised subjects who received any study medication and/or investigational product.

Study Population: Cytotoxic chemotherapy naïve male and female (of non-childbearing potential) subjects aged $\geq$18 years, scheduled to receive their first course of chemotherapy treatment for a malignant solid tumour with high-dose ($\geq$70mg/m^2) cisplatin-based regimen were recruited.

Number of Subjects:	**Control**	**Single Dose Oral**	**3-Day IV/Oral**
Planned, N	270	270	270

Randomised, N	269	271	270
Completed all Planned Chemotherapy, n (%)	171 (64)	165 (61)	172 (64)
Total Number Subjects Withdrawn, N (%)	98 (36)	106 (39)	98 (36)
Withdrawn due to Adverse Events n (%)	5 (2)	13 (5)	11 (4)
Withdrawn due to Lack of Efficacy n (%)	4 (1)	2 (<1)	3 (1)
Withdrawn for other reasons n (%)	89 (33)	91 (34)	84 (31)
Demographics	**Control**	**Single Dose Oral**	**3-Day IV/Oral**
N (ITT)	269	271	270
Females: Males	89:180	91:180	83:187
Mean Age, years (SD)	57.0 (10.84)	57.8 (10.63)	56.1 (11.44)
White, n (%)	187 (70)	192 (71)	182 (67)
Primary Efficacy Results:			
	Control	**Single Dose Oral**	**3-Day IV/Oral**
N (MITT)			
Complete Response 0-120 h, n (%)	175 (66)	228 (86)	214 (80)
Cochran-Mantel-Haenszel Test p-value		<0.0001	0.0004
Odds Ratio		3.07	2.00
97.5% CI		1.86, 5.06	1.28, 3.14
Secondary Outcome Variable(s):			
	Control	**Single Dose Oral**	**3-Day IV/Oral**
N (MITT)	265	266	269
Complete Response 0-24 h, n (%)	234 (88)	253 (95)	253 (94)
Odds Ratio		2.49	2.34
97.5% CI		1.14, 5.45	1.08, 6.06
Complete Response 24-120 h, n (%)	175 (66)	228 (86)	214 (80)
Odds Ratio		2.07	2.00
97.5% CI		1.86, 5.06	1.28, 3.14
Vomiting 0-120 h, n (%)	86 (32)	30 (11)	47 (17)
Odds Ratio		0.26	0.44
97.5% CI		0.16, 0.45	0.27, 0.70
Vomiting 0-24 h, n (%)	30 (11)	10 (4)	16 (6)
Odds Ratio		0.31	0.44
97.5% CI		0.13, 0.74	0.20, 0.96
Vomiting 24-120 h, n (%)	86 (32)	31 (11)	47 (17)
Odds Ratio		0.26	0.44
97.5% CI		0.16, 0.45	0.27, 0.70
Maximum Nausea Score (VAS) 0-120 hrs	n=265	n=264	n=266
Mean (SD)	24.6 (32.5)	14.6 (23.9)	16.8 (26.2)
Median (Min-Max)	7.0 (0-100)	3.0 (0-100)	3.0 (0-100)
Maximum Nausea Score (VAS) 0-24 hrs	n=226	n=216	n=226
Mean (SD)	11.4 (24.5)	5.4 (13.0)	5.1 (14.0)
Median (Min-Max)	1.0 (0-100)	1.0 (0-100)	1.0 (0-100)
Maximum Nausea Score (VAS) 24-120 hrs	n=264	n=264	n=266
Mean (SD)	23.1 (31.4)	13.8 (23.7)	16.1 (25.8)
Median (Min-Max)	5.0 (0-100)	3.0 (0-100)	3.0 (0-100)
Significant Nausea (VAS) 0-120 h, n (%)	81 (31)	59 (22)	64 (24)
Odds Ratio		0.65	0.71
97.5% CI		0.41, 1.02	0.45, 1.10
Significant Nausea (VAS) 0-24 h, n (%)	31 (12)	17 (6)	15 (6)
Odds Ratio		0.54	0.45

97.5% CI		0.26, 1.14	0.21, 0.97
Significant Nausea (VAS) 24-120 h, n (%)	81 (31)	59 (22)	64 (24)
Odds Ratio		0.65	0.71
97.5% CI		0.41, 1.02	0.45, 1.10
Nausea (VAS) 0-120 h, n (%)	144 (54)	115 (43)	122 (45)
Odds Ratio		0.64	0.69
97.5% CI		0.43, 0.95	0.47, 1.02
Nausea (VAS) 0-24 h, n (%)	60 (24)	44 (17)	44 (16)
Odds Ratio		0.62	0.61
97.5% CI		0.38, 1.03	0.37, 1.00
Nausea (VAS) 24-120 h, n (%)	144 (54)	115 (43)	122 (45)
Odds Ratio		0.64	0.69
97.5% CI		0.43, 0.95	0.47, 1.02
Maximum Nausea Severity (Categorical Scale) 0-120 h, n (%)			
None	124 (47)	163 (61)	153 (57)
Mild	64 (24)	52 (20)	52 (19)
Moderate	40 (15)	28 (11)	42 (16)
Severe	37 (14)	23 (9)	22 (8)
Maximum Nausea Severity (Categorical Scale) 0-24 h, n (%)			
None	208 (78)	229 (86)	227 (84)
Mild	32 (12)	23 (9)	25 (9)
Moderate	15 (6)	8 (3)	9 (3)
Severe	10 (4)	6 (2)	8 (3)
Maximum Nausea Severity (Categorical Scale) 24-120 h, n (%)			
None	124 (47)	163 (61)	153 (57)
Mild	64 (24)	52 (20)	52 (19)
Moderate	40 (15)	28 (11)	42 (16)
Severe	37 (14)	23 (9)	22 (8)
Complete Protection 0-120 h, n (%)	159 (60)	195 (73)	186 (69)
Odds Ratio		1.85	1.50
97.5% CI		1.21, 2.82	0.99, 2.26
Complete Protection 0-24 h, n (%)	218 (82)	242 (91)	246 (91)
Odds Ratio		2.18	2.30
97.5% CI		1.18, 4.03	1.23, 4.30
Complete Protection 24-120 h, n (%)	159 (60)	195 (73)	186 (69)
Odds Ratio		1.85	1.50
97.5% CI		1.21, 2.82	0.99, 2.26
Total Control 0-120 h, n (%)	118 (45)	147 (55)	142 (53)
Odds Ratio		1.54	1.40
97.5% CI		1.04, 2.29	0.95, 2.07
Total Control 0-24 h, n (%)	193 (73)	218 (82)	219 (81)
Odds Ratio		1.70	1.65
97.5% CI		1.05, 2.76	1.03, 2.66
Total Control 24-120 h, n (%)	118 (45)	147 (55)	142 (53)
Odds Ratio		1.54	1.40
97.5% CI		1.04, 2.29	0.95, 2.07
Complete Response 0-120 h in Cycle 2, n/N (%)	113/146 (77)	123/131 (94)	143/161 (89)
Complete Response 0-120 h in Cycle 3, n/N (%)	92/118 (78)	89/97 (92)	106122 (87)

Complete Response 0-120 h in Cycle 4, n/N (%)	66/89 (74)	70/75 (93)	67/76 (88)
Complete Response 0-120 h in Cycle 5, n/N (%)	13/15 (87)	10/11 (91)	5/6 (83)
Complete Response 0-120 h in Cycle 6, n/N (%)	5/9 (56)	8/8 (100)	3/5 (60)
Rescue Medication 0-120 h, n (%)	21 (8)	16 (6)	15 (6)
Odds Ratio		0.64	0.68
97.5% CI		0.28, 1.45	0.31, 1.52
Rescue Medication 0-24 h, n (%)	5 (2)	6 (2)	1 (<1)
Odds Ratio		1.15	0.34
97.5% CI		0.30, 4.40	0.03, 3.48
Rescue Medication 24-120 h, n (%)	21 (8)	16 (6)	15 (6)
Odds Ratio		0.64	0.68
97.5% CI		0.28, 1.45	0.31, 1.52
FLIE Scores 0-120 h			
Total FLIE	n=260	n=257	n=264
Mean (SD)	107.5 (26.2)	115.7 (18.2)	114.0 (21.2)
Nausea Subscore	n=261	n=258	n=264
Mean (SD)	52.6 (13.9)	56.2 (11.1)	55.6 (12.1)
Vomiting Subscore	n=260	n=257	n=264
Mean (SD)	54.9 (13.1)	59.5 (8.7)	58.4 (10.2)
Subject Satisfaction 0-120h, n (%)			
Very Satisfied	135 (51)	153 (58)	155 (58)
Somewhat Satisfied	74 (28)	74 (28)	70 (26)
Neither Satisfied or Dissatisfied	29 (11)	28 (11)	27 (10)
Somewhat Dissatisfied	14 (5)	4 (2)	7 (3)
Very Dissatisfied	8 (3)	1 (<1)	6 (2)
Missing	5 (2)	6 (2)	4 (1)
Subject Willingness 0-120 h, n (%)			
Definitely Would be Willing	145 (55)	162 (61)	159 (59)
Probably Would be Willing	62 (23)	66 (25)	70 (26)
Not Certain	40 (15)	21 (8)	25 (9)
Probably Would Not be Willing	7 (3)	8 (3)	5 (2)
Definitely Would Not be Willing	6 (2)	3 (1)	5 (2)
Missing	5 (2)	6 (2)	5 (2)
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.			
Most Frequent Adverse Events – On-Therapy	**Control**	**Single Dose Oral**	**3-Day IV/Oral**
N (Safety)	265	267	270
Subjects with any AE(s), n (%)	194 (73)	205 (77)	203 (75)
Neutropenia	80 (30)	83 (31)	108 (40)
Leukopenia	44 (17)	53 (20)	60 (22)
Anaemia	34 (13)	31 (12)	45 (17)
Thrombocytopenia	30 (11)	38 (14)	30 (11)
Constipation	30 (11)	34 (13)	21 (8)
Nausea	29 (11)	21 (8)	24 (9)
Anorexia	23 (9)	32 (12)	34 (13)
Fatigue	22 (8)	37 (14)	27 (10)
Asthenia	20 (8)	19 (7)	14 (5)
Diarrhoea	15 (6)	21 (8)	22 (8)
Vomiting	15 (6)	6 (2)	12 (4)

ALT increased	9 (3)	20 (7)	17 (6)
Hiccups	8 (3)	16 (6)	22 (8)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]			
N (Safety)	265	267	270
Subjects with any SAE, n (%) [related]- Includes both fatal and non-fatal events	28 (11)	44 (16)	44 (16)
Neutropenia	5 (2)	3 (1)	11 (4)
Dehydration	4 (2)	2 (<1) [1]	1 (<1)
Blood creatinine increased	3 (1) [1]	2 (<1)	1 (<1)
Thrombocytopenia	3 (1)	1 (<1)	2 (<1)
Renal failure	3 (1)	1 (<1)	0
Pulmonary embolism	2 (<1)	4 (1)	0
Pyrexia	2 (<1)	1 (<1)	1 (<1)
Hyperglycaemia	2 (<1) [1]	0	1 (<1) [1]
Dyspnoea	2 (<1)	0	0
Febrile neutropenia	1 (<1)	4 (1)	6 (2)
Hyponatraemia	1 (<1)	0	3 (1)
Leukopenia	0	3 (1)	4 (1)
Back pain	0	2 (<1)	0
Myocardial infarction	0	2 (<1) [1]	0
Pneumonia	0	1 (<1)	5 (2)
Anaemia	0	0	2 (<1)
Haemoptysis	0	0	2 (<1)
Diarrhoea	0	0	2 (<1)
Peripheral oedema	0	0	2 (<1)
Infection	1 (<1)	1 (<1)	
Urinary tract infection	1 (<1)		1 (<1)
Neutropenic sepsis	1 (<1)		
Oral fungal infection	1 (<1)		
Tuberculosis	1 (<1)		
Tachypnoea	1 (<1)		
Atrial fibrillation	1 (<1)		1 (<1)
Cardiorespiratory arrest	1 (<1)	1 (<1)	
Pericardial effusion	1 (<1)		
Supraventricular tachycardia	1 (<1)		
Vomiting	1 (<1)		
Arterial disorder	1 (<1)		
Hypotension	1 (<1)		
Iliac artery embolism	1 (<1)		
Superficial thrombophlebitis	1 (<1)		
Thrombosis	1 (<1)		
Increased blood urea	1 (<1)	1 (<1)	
Musculoskeletal chest pain	1 (<1)		
Hypoacusis	1 (<1)		
Humerus fracture	1 (<1)		
Overdose	1 (<1)		
Complete suicide	1 (<1)		
Disseminated intravascular coagulation		1 (<1)	
Haemorrhagic diathesis		1 (<1)	
Respiratory tract infection		1 (<1)	1 (<1)
Biliary tract infection		1 (<1)	
Cystitis		1 (<1)	
Pleural effusion		1 (<1)	

Haemothorax		1 (<1)	
Respiratory failure		1 (<1)	
Hypokalaemia		1 (<1)	1 (<1)
Cachexia		1 (<1)	
Unstable angina		1 (<1)	
Cardiac disorder		1 (<1)	
Cardiogenic shock		1 (<1)	
Food poisoning		1 (<1)	
Haematemesis		1 (<1)	
Ileus		1 (<1)	
Stomatitis		1 (<1)	
Catheter related complication		1 (<1)	
Deep vein thrombosis		1 (<1) [1]	
Peripheral embolism		1 (<1)	
Thrombophlebitis		1 (<1)	
Venous thrombosis		1 (<1)	
Increased hepatic enzyme		1 (<1) [1]	
Cerebral ischaemia		1 (<1)	1 (<1)
Cerebrovascular accident		1 (<1)	
Convulsion		1 (<1)	
Spinal cord disorder		1 (<1)	
Bronchitis			1 (<1)
Fungal Infection			1 (<1)
Oral candidiasis			1 (<1)
Pneumococcal sepsis			1 (<1)
Pyelonephritis			1 (<1)
Pleural effusion			1 (<1)
Hiccups			1 (<1)
Pneumothorax			1 (<1)
Productive cough			1 (<1)
Cardiac failure			1 (<1)
Colitis			1 (<1)
Enterocolitis			1 (<1)
Gastritis			1 (<1) [1]
Gastrointestinal haemorrhage			1 (<1) [1]
Asthenia			1 (<1)
Fatigue			1 (<1)
Multi-organ failure			1 (<1)
Sudden death			1 (<1)
Embolism			1 (<1)
Extrapyramidal disorder			1 (<1) [1]
Neurological symptom			1 (<1)
Polyneuropathy			1 (<1)
Deafness			1 (<1)
Metastases to central nervous system			1 (<1)
Deaths within 30 days n (%)			
Dead	9 (3)	14 (5)	7 (3)
Primary cause of death:			
Disease under study	2 (<1)	6 (2)	4 (1)
Hematologic toxicity	1 (<1)	1 (<1)	0
Non-hematological toxicity	3 (1)	1 (<1)	0
Other	3 (1)	6 (2)	3 (1)
Conclusion: All casopitant regimens (Single Dose Oral and 3-Day IV/Oral) were more effective than control (ondansetron and dexamethasone), in preventing CINV in subjects receiving cisplatin based HEC and demonstrated an acceptable			

safety profile.