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Study No.: NKV110721
Title: A Study of Single Dose Intravenous Casopitant in Combination with Ondansetron and Dexamethasone for the Prevention of Oxaliplatin-Induced Nausea and Vomiting.
Rationale: Previous studies support the use of NK-1 receptor antagonists in combination with other antiemetics to enhance control of chemotherapy induced nausea and vomiting (CINV). This Phase III study was designed to evaluate the safety and efficacy of single dose 90 mg IV casopitant given on Day 1 in combination with ondansetron and dexamethasone for prevention of CINV in colorectal cancer patients receiving oxaliplatin-based moderately emetogenic chemotherapy (MEC).
Phase: III
Study Period: Study start date (first subject first visit) 10 March 2008- study completion (last subject last visit) 13 April 2009
Study Design: Randomised, double-blind, active-controlled, 2-arm, parallel-group.
Centres: 89 centres in 11 countries recruited subjects: 55 centres in Europe, 30 in North America, and 4 in Korea.
Indication: CINV
Treatment: Subjects were randomised to the Control or Single-Dose IV group. Both 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. Investigational product was dosed as follows: Control, placebo IV on Day 1; Single Dose IV, casopitant 90 mg IV on Day 1.
Objectives: The primary objective was to demonstrate the superiority of Single-Dose 90 mg IV casopitant in combination with ondansetron and dexamethasone over Control (ondansetron and dexamethasone alone) in the prevention of emesis over the first 0-120 hours (overall phase) following initiation of the first cycle of oxaliplatin-based MEC.
Primary Outcome/Efficacy Variable: Complete response, defined as no vomiting/retching and no rescue therapy, in the overall phase following initiation of the first cycle of an oxaliplatin-based MEC regimen.
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 [VAS] or a categorical scale), complete protection (complete responders who had no significant nausea [<25mm on VAS]) and total control (complete responders who had no nausea [<5mm on VAS]) in the overall, acute and delayed phases; rescue medication use; time to first emetic event, rescue medication use and complete response failure; health outcomes measures (Functional Living Index Emesis [FLIE]). Efficacy in Cycle 2 was assessed by complete response (0-120 hours). Single-dose pharmacokinetic (PK) parameters for Cycle 1 included: AUC(0-∞), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2 for casopitant and metabolites GSK525060, GSK517142 and GSK631832; and CL (Clearance) and Vdss (Volume of distribution at steady state) for casopitant only. Safety and tolerability were assessed in all Cycles.
Statistical Methods: Assuming a 60% complete response rate for standard of care at 120 hours, 326 subjects per arm (652 subjects total) were required to show a 12% difference between standard of care and the investigational treatment arm with 90% power and a two-sided level of significance of 0.05. The primary efficacy analysis compared the Single Dose IV group with the Control group for the proportion of subjects achieving a complete response 0-120 hours in the modified intent-to treat (MITT) population (randomised subjects who received any investigational product and had oxaliplatin administered), using a pooled Z test. P-values, treatment differences and 95% confidence intervals (CI) were reported. If the primary endpoint result was significant ($p<0.05$), then the secondary endpoints of complete response (acute phase) then complete

response (delayed phase) were tested hierarchically at a significance level of 0.05. Treatment difference and 95% CIs were presented. Testing stopped when a hypothesis failed to meet significance. Secondary endpoints of rescue use, vomiting, significant nausea and nausea were compared among the treatment groups on the basis of odds ratios. Complete protection and total control were compared using the Pearson chi-square test. The VAS and categorical scale assessments of maximum nausea severity were analysed using a Wilcoxon Rank Sum test and Mantel-Haenszel chi-square test., respectively. The FLIE scores were assessed using the Wilcoxon rank sum test. Time to event endpoints were summarised using Kaplan-Meier survival curves and the treatment groups compared on the basis of a log-rank test. The safety population comprised all randomised subjects who received any investigational product. No statistical analysis of PK parameters was planned.

Study Population: Male and female (of non-childbearing potential) subjects aged ≥18 years, cytotoxic chemotherapy naïve (with the exception that prior (neo)adjuvant 5-FU/LV or capecitabine was permitted), scheduled to receive their first course of chemotherapy with oxaliplatin at a dose between 85-130 mg/m^2 administered as a single IV dose over 2-6 hours on Day 1 only, in combination with 5-FU/LV, or in combination with capecitabine in their first cycle of therapy for the treatment of colorectal cancer. Optionally, bevazicumab could have been added to either regimen.

Number of Subjects:	**Control**	**Single Dose IV**
Planned, N	350	350
Randomised, N	355	355
Completed 6 Cycles of Chemotherapy, n (%)	215 (61)	228 (64)
Total Number Subjects Withdrawn, N (%)	140 (39)	127 (36)
Withdrawn due to Adverse Events n (%)	43 (12)	32 (9)
Withdrawn due to Lack of Efficacy n (%)	11 (3)	12 (3)
Withdrawn for other reasons n (%)	86 (24)	83 (23)
Demographics	**Control**	**Single Dose IV**
N (ITT)	355	355
Females: Males	145:210	173:182
Mean Age, years (SD)	61.3 (10.77)	61.3 (11.03)
White, n (%)	326 (92)	318 (90)
Primary Efficacy Results:		
	Control	**Single Dose IV**
N (MITT)	352	355
Complete Response for Cycle 1, 0-120 h; n (%)	298 (85)	305 (86)
Treatment difference, %	1.0	
95% CI	-4.6, 6.6	
Z-score p-value	0.7273	
Secondary Outcome Variables:		
Cycle 1	**Control**	**Single Dose IV**
Complete Response, 0-24 h; n (%)	337 (96)	345 (97)
Treatment difference, %	1.0	
95% CI	-1.8, 3.8	
Complete Response, 24-120 h; n (%)	298 (85)	305 (86)
Treatment difference, %	1.0	
95% CI	-4.6, 6.6	
Vomiting, 0-120 h; n (%)	37 (11)	34 (10)
Treatment difference, %	-0.9	
95% CI	-5.4, 3.5	
Vomiting, 0-24 h; n (%)	10 (3)	7 (2)
Treatment difference, %	-0.9	
95% CI	-3.1, 1.4	

Vomiting, 24-120 h; n (%)	37 (11)	34 (10)
Treatment difference, %	-0.9	
95% CI	-5.4, 3.5	
Maximum Nausea Score (VAS) 0-120 h	n=349	n=353
Mean (SD)	13.5 (23.3)	16.0 (24.5)
Median (Min-Max)	2.0 (0-100)	3.0 (0-100)
Maximum Nausea Score (VAS) 0-24 h	n=286	n=288
Mean (SD)	4.3 (12.9)	5.3 (13.3)
Median (Min-Max)	1.0 (0-100)	1.0 (0-89)
Maximum Nausea Score (VAS) 24-120 h	n=349	n=352
Mean (SD)	13.0 (22.6)	15.3 (24.2)
Median (Min-Max)	2.0 (0-100)	3.0 (0-100)
Significant Nausea (VAS) 0-120 h, n (%)	66 (19)	74 (21)
Treatment difference, %	2.1	
95% CI	-3.8, 8.0	
Significant Nausea (VAS) 0-24 h, n (%)	15 (4)	18 (5)
Treatment difference, %	0.8	
95% CI	-2.3, 3.9	
Significant Nausea (VAS) 24-120 h, n (%)	66 (19)	74 (21)
Treatment difference, %	2.1	
95% CI	-3.8, 8.0	
Nausea (VAS) 0-120 h, n (%)	131 (37)	161 (45)
Treatment difference, %	8.1	
95% CI	0.9, 15.4	
Nausea (VAS) 0-24 h, n (%)	41 (12)	55 (15)
Treatment difference, %	3.8	
95% CI	-1.2, 8.9	
Nausea (VAS) 24-120 h, n (%)	131 (37)	161 (45)
Treatment difference, %	8.1	
95% CI	0.9, 15.4	
Maximum Nausea Severity (Categorical Scale) 0-120 h, n (%)		
None	218 (62)	192 (54)
Mild	73 (21)	97 (27)
Moderate	49 (14)	54 (15)
Severe	12 (3)	12 (3)
Maximum Nausea Severity (Categorical Scale) 0-24 h, n (%)		
None	313 (89)	299 (84)
Mild	23 (7)	40 (11)
Moderate	13 (4)	15 (4)
Severe	3 (1)	1 (<1)
Maximum Nausea Severity (Categorical Scale) 24-120 h, n (%)		
None	218 (62)	192 (54)
Mild	73 (21)	97 (27)
Moderate	49 (14)	54 (15)
Severe	12 (3)	12 (3)
Rescue medication 0-120 h, n (%)	33 (9)	27 (8)
Treatment difference, %	-1.8	
95% CI	-5.9, 2.3	
Rescue medication 0-24 h, n (%)	7 (2)	4 (1)

Treatment difference, %	-0.9	
95% CI	-2.7, 1.0	
Rescue medication 24-120 h, n (%)	33 (9)	27 (8)
Treatment difference, %	-1.8	
95% CI	-5.9, 2.3	
Complete Protection 0-120 h, n (%)	264 (75)	263 (74)
Treatment difference, %	-0.9	
95% CI	-7.3, 5.5	
Complete Protection 0-24 h, n (%)	329 (93)	330 (93)
Treatment difference, %	0.5	
95% CI	-3.2, 4.2	
Complete Protection 24-120 h, n (%)	264 (75)	263 (74)
Treatment difference, %	-0.9	
95% CI	-7.3, 5.5	
Total Control 0-120 h, n (%)	214 (61)	190 (54)
Treatment difference, %	-7.3	
95% CI	-15.0, 0.0	
Total Control 0-24 h, n (%)	308 (88)	294 (83)
Treatment difference, %	-4.7	
95% CI	-9.9, 0.5	
Total Control 24-120 h, n (%)	214 (61)	190 (54)
Treatment difference, %	-7.3	
95% CI	-15.0, 0.0	
Time to emesis: Hazard ratio (95% CI)	0.9 (0.6, 1.4)	
Time to rescue: Hazard ratio (95% CI)	0.8 (0.5, 1.3)	
Time to complete response failure: Hazard ratio (95% CI)	0.9 (0.7, 1.2)	
Complete Response for Cycle 2, 0-120 h; n/N (%)	274/328 (84)	302/337 (90)
Treatment difference, %	6.0	
95% CI	0.5, 11.5	

FLIE Scores 0-120 h		
Total FLIE	n=344	n=335
Mean (SD)	117.6 (15.1)	116.8 (14.8)
Nausea Subscore	n=344	n=343
Mean (SD)	57.3 (10.0)	56.6 (10.4)
Vomiting Subscore	n=334	n=336
Mean (SD)	60.1 (6.9)	60.2 (6.7)
PK Results:		
	Single Dose IV	
Plasma Casopitant PK parameters	n=25	
Cmax (ng/ml); geometric mean (CVb%)	1888 (83)	
Tmax (h); median (range)	0.52 (0.50, 1.5)	
AUC(0-24) (ng.h/mL); geometric mean (CVb%)	6715 (39.1)	
AUC(0-∞) (ng.h/mL); geometric mean (CVb%)	8386 (43.8)	
T1/2 (h); geometric mean (CVb%)	11.6 (36.5)	
CL (L/h); geometric mean (CVb%)	10.7 (43.8)	
Vdss (L); geometric mean (CVb%)	134 (48.1)	
Plasma GSK525060 PK parameters	n=25	
Cmax (ng/ml); geometric mean (CVb%)	147 (30.8)	
Tmax (h); median (range)	3.58 (1.00-24.5)	
AUC(0-24) (ng.h/mL); geometric mean (CVb%)	2340 (33.9)	
AUC(0t) (ng. h/mL); geometric mean (CVb%)	2882 (35.5)	
Plasma GSK517142 PK parameters	n=25	
Cmax (ng/ml); geometric mean (CVb%)	3.55 (42.3)	
Tmax (h); median (range)	1.50 (0.58-24.50)	
AUC(0-24) (ng.h/mL); geometric mean (CVb%)	49.9 (39.0)	
AUC(0t) (ng. h/mL); geometric mean (CVb%)	41.4 (122)	
Plasma GSK631832 PK parameters	n=25	
Cmax (ng/ml); geometric mean (CVb%)	10.1 (36.5)	
Tmax (h); median (range)	8.50 (3.48-24.67)	
AUC(0-24) (ng.h/mL); geometric mean (CVb%)	172 (37.5)	
AUC(0-t) (ng.h/mL); geometric mean (CVb%)	235 (41.9)	
Safety Results: Adverse events (AEs) and serious adverse events (SAEs) with onset following the first dose, until 28 days after the last dose, of study medication (ondansetron/dexamethasone) or study medication (casopitant/placebo) were collected. SAEs that were related to study participation (e.g., procedures, invasive tests, etc.) or were related to a GSK concurrent medication were collected and recorded from the time the subject consented to participate in the study.		
	Control	**Single Dose IV**
N (Safety)	352	355
Adverse Events (Most frequent 10 events in each group)	**n (%)**	**n (%)**
Subjects with any AEs	288 (82)	296 (83)
Neutropenia	94 (27)	110 (31)
Diarrhoea	75 (21)	98 (28)
Nausea	74 (21)	88 (25)
Fatigue	56 (16)	53 (15)
Constipation	39 (11)	39 (11)
Paraesthesia	36 (10)	24 (7)
Vomiting	35 (10)	16 (5)
Peripheral sensory neuropathy	33 (9)	47 (13)
Anorexia	30 (9)	25 (7)

Neuropathy peripheral	29 (8)	30 (8)
Thrombocytopenia	25 (7)	38 (11)
Headache	18 (5)	26 (7)
Serious Adverse Events n (%) [n considered by the investigator to be related to study medication]		
	Control	**Single Dose IV**
N (Safety)	352	355
Subjects with any SAE, n (%) [related]-Includes both fatal and non-fatal events	23 (7)	26 (7)
Diarrhoea	3 (<1)	3 (<1)
Pulmonary embolism	2 (<1)	3 (<1)
Intestinal obstruction	2 (<1)	2 (<1) [1]*
Deep vein thrombosis	2 (<1)	2 (<1)
Ileus	2 (<1)	1 (<1)
Pneumonia	1 (<1)	2 (<1)
Rectal haemorrhage	1 (<1)	1 <1)
Angina unstable	1 (<1)	1 (<1)
Hypovolaemic shock	1 (<1)	0
Venous thrombosis	1 (<1)	0
Atrial fibrillation	1 (<1)	0
Atrioventricular block complete	1 (<1)	0
Cardiovascular disorder	1 (<1)	0
Tachycardia	1 (<1)	0
Bronchitis	1 (<1)	0
Catheter related infection	1 (<1)	0
Sudden death	1 (<1)	0
Cerebral ischaemia	1 (<1)	0
Transient ischaemic attack	1 (<1)	0
Dehydration	1 (<1)	0
Abdominal pain	0	2 (<1)
Thrombosis	0	2 (<1)
Infection	0	2 (<1)
Neutropenia	0	2 (<1)
Pyrexia	0	2 (<1)
Constipation	0	1 (<1)
Duodenal ulcer	0	1 (<1)
Gastritis	0	1 (<1)
Gastrointestinal obstruction	0	1 (<1)
Hypertensive crisis	0	1 (<1)
Hypotension	0	1 (<1)
Orthostatic hypotension	0	1 (<1)
Angina pectoris	0	1 (<1)
Cardiac failure	0	1 (<1)
Cardiopulmonary failure	0	1 (<1)
Febrile infection	0	1 (<1)
Pancytopenia	0	1 (<1)
Musculoskeletal pain	0	1 (<1)
Tumour compression	0	1 (<1)
Ureteric stenosis	0	1 (<1)
* Considered by the investigator to be related to ondansetron		

Subjects with fatal SAEs, n (%) [related]	3 (<1)	2 (<1)
Sudden death	1 (<1)	0
Hypovolaemic shock	1 (<1)	0
Cardiovascular disorder	1 (<1)	0
Cardiopulmonary failure	0	1 (<1)
Pulmonary embolism	0	1 (<1)

Conclusion: A significant improvement in the control of CINV after oxaliplatin-MEC was not demonstrated based on complete response (0-120 hours) in Cycle 1. Single-dose 90 mg IV casopitant was well tolerated. The most frequently reported AEs in both treatment groups were neutropenia and diarrhoea. The incidence of neutropenia was similar between groups. Diarrhoea was more common in the Single Dose IV group, mainly due to more Grade 1 events. Of the other common AEs, peripheral sensory neuropathy was more frequent in the Single Dose IV group, mainly due to more Grade 1 events, whereas paresthesia was more frequent in the Control group, mainly due to more Grade 2 events. The incidence of non-fatal and fatal SAEs was generally similar between groups. Across the entire safety database there were no notable differences in the incidence of cardiac or thrombotic adverse events.
The plasma casopitant AUC(0-∞) following administration of 90 mg IV casopitant was similar to that following 150 mg oral casopitant in CINV patients in previous studies. However, the plasma casopitant concentration 24 h post-dose was 24% lower and the plasma exposure of the major metabolite (GSK525060) was 48% lower following 90 mg IV administration compared with 150 mg oral administration.

Publications: None