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Study No.: 102260
Title: A multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel group phase II study to evaluate the safety, efficacy, and pharmacokinetics of an oral New Chemical Entity (NCE) when administered with intravenous ondansetron hydrochloride for the prevention of post-operative nausea and vomiting (PONV) and post-discharge nausea and vomiting (PDNV) in female subjects with known risk factors for PONV who are undergoing surgical procedures associated with an increased emetogenic risk.
Rationale: The aim of this study was to evaluate whether the addition of a single oral dose of a NCE would improve the antiemetic efficacy of a single intravenous 4 mg dose of ondansetron hydrochloride, when both were administered prior to the induction of anesthesia. This summary includes results for the placebo NCE + ondansetron arm. Results for the NCE treatment arms of the study will be added, if and when the NCE is approved and marketed.
Phase: II
Study Period: 22 October 2004 to 08 August 2005
Study Design: A multicenter, randomized, double-blind, placebo-controlled, parallel group study.
Centers: 55 centers in Belgium (4), Canada (12), Germany (2), Hungary (3), Spain (3), and the United States (31).
Indication: Post-operative nausea and vomiting (PONV).
Treatment: All eligible subjects received a NCE, 60 minutes prior to the induction of anesthesia. Subjects were randomized (1:1:1:1:1) to oral NCE (either active or placebo) together with a single intravenous administration (over 2-5 minutes) of ondansetron hydrochloride (HCl) (either active or placebo) as follows: Cohort A: Placebo NCE + 4 mg Ondansetron HCl Cohort B: NCE dose level 1 + 4 mg Ondansetron HCl Cohort C: NCE dose level 2 + 4 mg Ondansetron HCl Cohort D: NCE dose level 3 + 4 mg Ondansetron HCl Cohort E: NCE dose level 3 + Placebo Ondansetron HCl Subjects were to be assessed for up to 5 days after emergence from anesthesia.
Objectives: The primary objective was to determine the optimal single dose of oral NCE when administered in combination with intravenous ondansetron HCl for the prevention of emesis (defined as vomiting or retching) during the first 24 hours following the emergence from anesthesia in female subjects with known risk factors for PONV who were undergoing surgical procedures that are associated with an increased emetogenic risk.
Primary Outcome/Efficacy Variable: The primary efficacy variable was to assess the number of subjects who achieved a complete response (CR), defined as no vomiting, no retching, no rescue therapy, and no premature discontinuation from the study during the first 24 hour evaluation period following emergence from anesthesia.
Secondary Outcome/Efficacy Variable(s): The secondary efficacy variables were: CR at 48, 72, 96 and 120 hours following emergence from anesthesia. Extent of nausea experienced by subjects during the 2, 6, 24, 48, 72, 96 and 120 hour evaluation periods following the emergence from anesthesia, as assessed by a discrete Likert scale. Extent of pain experienced by subjects during the 2, 6, 24, 48, 72, 96 and 120 hour evaluation periods following the emergence from anesthesia, as assessed by a discrete Likert scale. Impact on daily life activities as assessed by the FLIE. Subject satisfaction with study medication. Subject willingness to use study medication. Time to first emetic event, defined as the length of time from emergence from anesthesia until the time of the first emetic event;. Time to rescue medication, defined as the length of time from emergence from anesthesia until the time of the first rescue medication.
Statistical Methods: The primary population of interest was the intent-to-treat (ITT) population which was used for the analysis of efficacy data. The ITT population was defined as all subjects who were randomized to 1 of 5 treatment regimens. The safety population comprised all subjects who received any study medication. The Cochran–Armitage trend test was used to detect a monotonic dose response.
Study Population: Non-pregnant, non-lactating female subjects using adequate contraception were eligible if they were: pre-menopausal or peri-menopausal between the ages of 18-55 years; not of childbearing potential; had never smoked or used (e.g. chewing) tobacco, or had successfully quit smoking and/or using tobacco and had been a non-

smoker and non-user (including a nicotine patch) for at least the previous 12 consecutive months; had a known history of post-operative nausea and vomiting and/or motion sickness; were undergoing a laparoscopic/laparotomic gynecological surgical procedure or laparoscopic cholecystectomy that was scheduled for no less than 1 hour in duration and no longer than 3 hours in duration; was scheduled to receive general anesthesia with an anesthetic regimen as described in the Anesthetic Regimen; met the American Society of Anesthesiologists (ASA) Physical Status Classification of I or II preoperatively on the day of surgery; had hematology and blood chemistry values within acceptable limits [i.e. within 10% outside (either above or below) normal reference values, unless otherwise specified] for surgery, including, but not limited to hemoglobin, hematocrit, total white blood cell count, platelet counts, alkaline phosphatase, blood urea nitrogen or serum urea, electrolytes (sodium, potassium, chloride, bicarbonate), liver function tests (alanine aminotransferase and aspartate aminotransferase <1.5 times the upper limit of normal [ULN]), serum creatinine (<1.5 times ULN), total bilirubin (<1.5 times ULN); were able and willing to complete daily components of the subject diary preoperatively on the day of surgery and until the end of the 120-hour follow-up assessment period, and were available to respond to follow-up by study personnel at the 120-hour study period post-emergence from anesthesia; and understood the nature and purpose of the study and the study procedures.

Subjects were excluded from this study if they: met ASA Physical Status Classification of III, IV, or V preoperatively on the day of surgery; were scheduled to undergo a laparoscopic biopsy; were scheduled to receive neuroaxial anesthesia (e.g. epidural, spinal, or caudal anesthesia) or total intravenous volatile anesthesia; were scheduled to receive propofol for maintenance of anesthesia; were scheduled to have gastric contents suctioned continuously during the surgical procedure via a nasogastric tube, or a nasogastric or oral gastric tube during the post-operative period (a single pass at the beginning or at the end of the surgical procedure, and intraoperative gastric suctioning of air, were permitted); had been taking more than 10 to 15mg of oxycodone, or an equivalent opioid dose, on a regular, daily basis, for more than 3 consecutive days in the week prior to surgery; had persistent or recurrent nausea and/or vomiting due to other etiologies, including, but not limited to, gastric outlet obstruction, hypercalcemia, active peptic ulcer, increased intracranial pressure, or brain metastases; had experienced retching or vomiting or uncontrolled nausea within 48 hours prior to administration of study drug; had experienced significant nausea (e.g. ≥3 units on a discrete Likert scale) in the 24-hour period prior to receiving the dose of the NCE study medication; had received radiation therapy to the abdomen or the pelvis in the 7 days prior to receiving study medication and/or were to receive radiation therapy to the abdomen or the pelvis in the evaluation period; had a history of wound dehiscence; had a history of previous or current peptic ulceration or inflammatory bowel disease; had received medication with known or potential antiemetic activity within the 24-hour period prior to receiving study drug, including, had taken/received strong or moderate inhibitors of cytochrome P450 isoenzymes (CYP), CYP3A4 and CYP3A5, within 14 days prior to study drug administration.

	Placebo NCE + 4mg ondansetron HCl
Number of Subjects:	
Planned, N	117
Randomized, N	140
Completed, n (%)	129 (92)
Total Number Subjects Withdrawn, n (%)	11 (8)
Withdrawn due to Adverse Events, n (%)	0
Withdrawn due to Lack of Efficacy, n (%)	0
Withdrawn for Other Reasons, n (%)	11 (8)
Demographics:	**Placebo NCE + 4mg ondansetron HCl**
N (ITT)	140
Females, n	140
Mean Age, years (standard deviation [SD])	39.3 (8.15)
Not Hispanic or Latino, n (%)	121 (86)
Primary Efficacy Results: (ITT Population) This summary includes results for the placebo NCE + ondansetron arm. Results for the NCE treatment arms of the study will be added, if and when the NCE is approved and marketed.	
Complete response (0-24 hours)	**Placebo NCE + 4mg ondansetron HCl (N=140)**
Subjects with complete response, n (%)	56 (40.0)
Secondary Outcome Variable(s): (ITT Population)	
	Placebo NCE + 4mg ondansetron HCl (N=140)
Complete response:	

Subjects with complete response at 0-48 hours, n (%)	53 (37.9)
Subjects with complete response at 0-72 hours, n (%)	53 (37.9)
Subjects with complete response at 0-96 hours, n (%)	52 (37.1)
Subjects with complete response at 0-120 hours, n (%)	51 (36.4)
Significant nausea[b]:	
Subjects with significant nausea at 0-2 hours, n (%)	44 (31.4)
Subjects with significant nausea at 0-6 hours, n (%)	69 (49.3)
Subjects with significant nausea at 0-24 hours, n (%)	88 (62.9)
Subjects with significant nausea at 0-48 hours, n (%)	95 (67.9)
Subjects with significant nausea at 0-72 hours, n (%)	96 (68.6)
Subjects with significant nausea at 0-96 hours, n (%)	96 (68.6)
Subjects with significant nausea at 0-120 hours, n (%)	98 (70.0)
[b] ≥3 units on a discrete Likert scale.	
Nausea:	
Subjects with nausea at 0-2 hours, n (%)	49 (35.0)
Subjects with nausea at 0-6 hours, n (%)	74 (52.9)
Subjects with nausea at 0-24 hours, n (%)	94 (67.1)
Subjects with nausea at 0-48 hours, n (%)	99 (70.7)
Subjects with nausea at 0-72 hours, n (%)	100 (71.4)
Subjects with nausea at 0-96 hours, n (%)	101 (72.1)
Subjects with nausea at 0-120 hours, n (%)	103 (73.6)
Significant pain[c]:	
Subjects with significant pain at 0-2 hours, n (%)	91 (65.0)
Subjects with significant pain at 0-6 hours, n (%)	111 (79.3)
Subjects with significant pain at 0-24 hours, n (%)	118 (84.3)
Subjects with significant pain at 0-48 hours, n (%)	121 (86.4)
Subjects with significant pain at 0-72 hours, n (%)	122 (87.1)
Subjects with significant pain at 0-96 hours, n (%)	122 (87.1)
Subjects with significant pain at 0-120 hours, n (%)	123 (87.9)
[c] ≥3 units on a discrete Likert scale.	
Pain:	
Subjects with pain at 0-2 hours, n (%)	97 (69.3)
Subjects with pain at 0-6 hours, n (%)	116 (82.9)
Subjects with pain at 0-24 hours, n (%)	122 (87.1)
Subjects with pain at 0-48 hours, n (%)	123 (87.9)
Subjects with pain at 0-72 hours, n (%)	124 (88.6)
Subjects with pain at 0-96 hours, n (%)	124 (88.6)
Subjects with pain at 0-120 hours, n (%)	125 (89.3)
Time to emesis, hours:	
Subjects with event, n (%)	51 (36.4)
1st Quartile (95% CI)	19.6 (6.5, 48.0)
Time to rescue:	
Subjects with event, n (%)	64 (45.7)
1st Quartile (95% CI)	4.6 (1.7, 7.8)
FLIE scores (0-120 hours):	
n	119
Mean nausea score (SD)	10.3 (0.8)
Mean vomiting score (SD)	10.0 (0.8)
Mean total score (SD)	20.4 (1.6)
FLIE interpretations (0-120 hours), n (%):	
n	119
Did PONV impact your life?	119 (100)
Did nausea impact your life?	119 (100)
Did vomiting impact your life?	119 (100)
Subject satisfaction (0-120 hours), n (%):	

Very satisfied	74 (53)
Somewhat satisfied	18 (13)
Neither satisfied nor dissatisfied	14 (10)
Somewhat dissatisfied	7 (5)
Very dissatisfied	6 (4)
Subject willingness (0-120 hours), n (%):	
Definitely would be willing	69 (49)
Probably would be willing	26 (19)
Not certain	17 (12)
Probably would be willing	3 (2)
Definitely would not be willing	4 (3)
NC Not calculable.	
Safety Results: (Safety Population) - Adverse events (AEs) and serious adverse events (SAEs) were reported from the time of initial prophylactic study drug administration for up to 5 days after emergence from anesthesia (i.e. for the duration of the 120-hour follow-up assessment phase). This summary includes results for the placebo NCE + ondansetron arm. Results for the NCE treatment arms of the study will be added, if and when the NCE is approved and marketed.	
	Placebo NCE + 4mg ondansetron HCl (N=130)
Most Frequent Adverse Events	**n (%)**
Subjects with any AE(s), n (%)	68 (52)
Headache	16 (12)
Constipation	13 (10)
Dizziness	8 (6)
Pruritus	8 (6)
Flatulence	7 (5)
Hypotension	4 (3)
Insomnia	4 (3)
Abdominal distension	3 (2)
Diarrhoea	3 (2)
Pyrexia	3 (2)
Oxygen saturation decreased	3 (2)
Urinary retention	3 (2)
Serious Adverse Events **n (%) [n considered by the investigator to be related to study medication]**	
	Placebo NCE + 4mg ondansetron HCl (N=130)
Subjects with any SAEs, n (%)	4 (3) [1]
	n (%) [related]
Bladder spasm	1 (<1) [0]
Deep vein thrombosis	1 (<1) [0]
Hemorrhage	1 (<1) [1]
Nausea	1 (<1) [0]
Urinary tract infection	1 (<1) [0]
Vomiting	1 (<1) [0]
Subjects with fatal SAEs, n (%)	0

Conclusion: This study showed that 56 (40%) subjects showed a complete response from 0-24 hours in the placebo NCE + 4mg ondansetron HCl group. In total, 68 (52%) subjects reported AEs in the placebo NCE + 4mg ondansetron HCl group with the most frequently reported AEs being headache and constipation. Four (3%) of subjects reported SAEs, no SAE was reported in more than 1 subject. No fatal SAEs were reported.
Publications: No publication

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