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.: 102245
Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase II Study to Evaluate the Safety and Efficacy of Oral Dosing With a New Chemical Entity (NCE) for Three Consecutive Days when Administered with a Single Intravenous Dose of Ondansetron Hydrochloride for the Prevention of Postoperative Nausea and Vomiting and Post-discharge Nausea and Vomiting in Female Subjects with Known Risk Factors for Postoperative Nausea and Vomiting Who Were Undergoing Laparoscopic/Laparotomic Surgical Procedures Associated with an Increased Emetogenic Risk
Rationale: The aim of this study was to evaluate whether the addition of oral doses of an NCE for three days would improve the anti-emetic efficacy of a single intravenous 4 mg dose of ondansetron hydrochloride administered on the day of surgery. 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: 15 Feb 2005 to 23 Aug 2005
Study Design: Multicenter, randomized, double-blind, placebo-controlled, parallel-group study.
Centres: 39 sites in 10 countries (United Kingdom, United States, Denmark, Slovenia, Norway, Hungary, Spain, Thailand, Hong Kong, and Phillippines)
Indication: Postoperative and post-discharge nausea and vomiting
Treatment: On the day of surgery (Day 1), all subjects were to receive their first dose of NCE (active drug or placebo) with as little water as possible 30-60 minutes prior to the induction of anesthesia. Ondansetron hydrochloride 4mg was to be administered IV over 2 to 5 minutes immediately prior to the induction of anesthesia. On Days 2 and 3, the NCE dose was to be taken at approximately the same time the subject awoke from anesthesia on Day 1.
Objectives: To determine the antiemetic dose of oral NCE when administered for 3 consecutive days in combination with a single IV dose of 4 mg ondansetron hydrochloride administered on the day of surgery that provides incremental improvement in the prevention of emesis (defined as vomiting or retching) during the first 72 hours following the emergence from anesthesia in female subjects undergoing laparoscopic/laparotomic surgical procedures who are predicted to have a high emetogenic risk.
Primary Outcome/Efficacy Variable: 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 first 72-hour (3-day) evaluation period following the subject's emergence from anesthesia.
Secondary Outcome/Efficacy Variables: The proportion of subjects who achieved a complete response during each subsequent 24-hour evaluation period (up to 120 hours) following the emergence from anesthesia. The extent of nausea experienced by subjects during the 2-, 6-, and 24-hour evaluation periods as well as each subsequent 24-hour evaluation period (up to 120 hours) following the emergence from anesthesia, as assessed by a visual analogue scale (VAS). Time to emesis, time to rescue, time to awakening, and time to readiness for discharge. Subjects' satisfaction with the control of PONV/PDNV and the duration of control of PONV/PDNV by the prophylactic antiemetic regimen administered, and the willingness of subjects to use the same antiemetic drug treatment regimen for future surgical procedures. The extent of pain experienced by subjects during the 2-, 6-, and 24-hour evaluation periods, and each subsequent 24-hour evaluation period (up to 120 hours), following the emergence from anesthesia, as assessed by VAS. Safety and tolerability assessments, including routine physical exam findings, vital signs, electrocardiogram (ECG) monitoring, routine clinical laboratory tests, clinical monitoring and/or observation (including time to awakening from anesthesia and time to readiness for discharge), and adverse event (AE) reporting.
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 3 treatment regimens. The safety population comprised all subjects who received any study medication. For the primary endpoint, the Cochran-Armitage Trend Test was used for testing the hypothesis of no dose response. .
Study Population: Premenopausal or perimenopausal women who were scheduled to undergo a 1- to 3 hour laparoscopic/laparotomic surgical procedure (either gynecologic surgery or cholecystectomy) under general inhalational anesthesia. Eligible subjects had to have an American Society of Anesthesiologists (ASA) Physical Status Classification of I (normal, healthy patient) or II (patient with mild systemic disease) preoperatively on the day of

surgery and a history of postoperative nausea and vomiting and/or motion sickness. In addition, subjects were not to have smoked or used tobacco (including chewing tobacco, nicotine patches or other nicotine-withdrawal formulations) for the previous 12 months.

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 pregnant or lactating; were postmenopausal; were scheduled to undergo only a laparoscopic biopsy; were scheduled to receive neuroaxial anesthesia (e.g., epidural, spinal, or caudal anesthesia) or total IV anesthesia; were scheduled to receive propofol for maintenance of anesthesia; were expected to have gastric contents suctioned throughout the surgical procedure via a nasogastric tube, or a nasogastric or oral gastric tube during the postoperative period; had been taking more than 10 – 15 mg of oxycodone, or an equivalent opioid dose, on a regular daily basis, for more than 3 consecutive days during the week prior to surgery; had received an investigational drug in the previous 30 days or was scheduled to receive any investigational drug in addition to GW679769 during the study period; 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 the investigational product; had experienced significant nausea (e.g., $\geq$ 25 mm on a visual analogue scale [VAS]) in the 24-hour period prior to receiving the investigational product; had received radiation therapy to the abdomen or pelvis in the 7 days prior to receiving the investigational product and/or were to receive radiation therapy to the abdomen or pelvis during the evaluation period; had a history of wound dehiscence; had a history of any other illness which, in the opinion of the investigator, could pose an unacceptable risk by administration of the investigational product; had any current or past medical condition (e.g., vagotomy) and/or required medication to treat a condition that could confound the evaluation of the data collected in this clinical trial; had a known hypersensitivity or contraindication to ondansetron hydrochloride or ondansetron, another 5-HT3 receptor antagonist, any scheduled anesthetic or analgesic agents, or any component of GW679769; had a known hypersensitivity to fentanyl and/or ketorolac tromethamine; had a known allergy to eggs or egg products; were scheduled to receive antiemetics not outlined in the study dosing scheme; had received medication with known or potential antiemetic activity within the 24 hour period prior to receiving the investigational product; had taken strong or moderate inhibitors of CYP3A4 and CYP3A5 within specified periods prior to administration of the investigational product; had taken inducers of CYP3A4 and CYP3A5 within 14 days prior to the administration of the investigational product, including: carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort, and troglitazone; had previously received an NK-1 receptor antagonist.

	Placebo NCE + 4mg ondansetron HCl
Number of Subjects:	
Planned, N	147
Randomized, N	146
Completed, n (%)	136
Total Number Subjects Withdrawn, n (%)	10
Withdrawn due to Adverse Events, n (%)	2 (1)
Withdrawn due to Lack of Efficacy, n (%)	0
Withdrawn for Other Reasons, n (%)	8 (5%)
Demographics:	**Placebo NCE + 4mg ondansetron HCl**
N (ITT)	146
Females, n	146 (100)
Mean Age, years (standard deviation [SD])	41.3 (7.2)
Not Hispanic or Latino, n (%)	143 (98)
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 (0-72 hours)	**Placebo NCE + 4mg ondansetron HCl (N=146)**
Subjects with complete response, n (%)	68 (46.6)
Secondary Outcome Variable(s): (ITT Population)	
Complete response:	
Subjects with complete response at 0-24 hours, n (%)	42 (57.5)
Subjects with complete response at 0-48 hours, n (%)	70 (47.9)
Subjects with complete response at 0-96 hours, n (%)	67 (45.9)
Subjects with complete response at 0-120 hours, n (%)	67 (45.9)
Significant nausea[a]:	

Subjects with significant nausea at 0-2 hours, n (%)	60 (41.1)
Subjects with significant nausea at 0-6 hours, n (%)	76 (52.1)
Subjects with significant nausea at 0-24 hours, n (%)	87 (59.6)
[a] ≥3 units on a discrete Likert scale.	
Nausea:	
Subjects with nausea at 0-2 hours, n (%)	73 (50)
Subjects with nausea at 0-6 hours, n (%)	95 (65.1)
Subjects with nausea at 0-24 hours, n (%)	109 (74.7)
Significant pain[b]:	
Subjects with significant pain at 0-2 hours, n (%)	120 (82.2)
Subjects with significant pain at 0-6 hours, n (%)	128 (87.7)
Subjects with significant pain at 0-24 hours, n (%)	135 (92.2)
[b] ≥3 units on a discrete Likert scale.	
Pain:	
Subjects with pain at 0-2 hours, n (%)	135 (92.5)
Subjects with pain at 0-6 hours, n (%)	140 (95.9)
Subjects with pain at 0-24 hours, n (%)	142 (97.3)
Time to emesis, hours:	
Subjects with event, n (%)	59 (40.4)
1st Quartile (95% CI)	7.6 (5.1, 21.0)
Median	NE
Time to rescue:	
Subjects with event, n (%)	43 (29.5)
1st Quartile (95% CI)	19 (9.4, NE)
Median	NE
Subject satisfaction (0-120 hours), n (%):	
Very satisfied	82 (56)
Somewhat satisfied	34 (23)
Neither satisfied nor dissatisfied	15 (10)
Somewhat dissatisfied	5 (3)
Very dissatisfied	2 (1)
Subject willingness (0-120 hours), n (%):	
Definitely would be willing	78 (53)
Probably would be willing	40 (27)
Not certain	16 (11)
Probably would be willing	3 (2)
Definitely would not be willing	2 (1)
NE = not evaluable.	
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).	
	Placebo NCE + 4mg ondansetron HCl (N=141)
Most Frequent Adverse Events	**n (%)**
Subjects with any AE(s), n (%)	45 (32)
Pyrexia	9 (6)
Constipation	7 (5)
Dizziness	5 (4)
Headache	4 (3)
Pruritus	4 (3)
Urinary Tract Infection	3 (2)
Asthenia	2 (1)
Alanine aminotransferase increased	2 (1)
Back pain	2 (1)
Cough	2 (1)

Dyspepsia	2 (1)
Dyspnea	2 (1)
Dysuria	2 (1)
Fatigue	2 (1)
Insomnia	2 (1)
Liver Function Test abnormal	2 (1)
Post-procedural hemorrhage	2 (1)
Seasonal allergy	2 (1)
Upper Respiratory Tract infection	2 (1)
Wound Secretion	2 (1)
Serious Adverse Events **n (%) [n considered by the investigator to be related to study medication]**	
	Placebo NCE + 4mg ondansetron HCl (N=141)
Subjects with any SAEs, n (%) [drug related]	2 (1) [0]
	n (%) [related]
Atalectasis	1 (<1) [0]
Dyspnea	1 (<1) [0]
Hypoxia	1 (<1) [0]
Conclusion: This study showed that 75 (51.4%) subjects showed a complete response from 0-72 hours in the placebo NCE + 4mg ondansetron HCl group. In total, 45 (32%) subjects reported AEs in the placebo NCE + 4mg ondansetron HCl group with the most frequently reported AEs being pyrexia and constipation. Two (2) subjects (1%) reported SAEs, none of which were considered by the investigator to be drug related. There were no deaths in this study. Within 1 year after study completion this section will either refer you to a publication or contain text interpreting the trial results.	
Publications: No publication	

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