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: VNK115640.

Title: A Multicenter, Randomized, Single-blind, Active-controlled, Parallel Group, Phase II Study to Evaluate the Efficacy, Safety, and Tolerability of a Single Intravenous (6 mg, 12 mg, 18 mg, 24 mg or 36 mg) Dose of the Neurokinin-1 Receptor Antagonist, Vestipitant (GW597599), Compared with a Single 4 mg Intravenous Ondansetron Hydrochloride Dose for the Treatment of Breakthrough Post-Operative Nausea and Vomiting after Failed Prophylaxis with an Ondansetron-Containing Regimen in Patients Undergoing Non-Emergency Surgical Procedures.

Rationale: Vestipitant (GW597599) is a potent and selective neurokinin 1 (NK1) receptor antagonist that has previously been investigated in 30 Phase I studies (clinical pharmacology studies) and 9 Phase II studies for various indications. In previous clinical studies, 2054 subjects have been exposed to vestipitant at dose levels ranging from 1 to 100 mg (oral) and 0.5 to 48 mg (intravenous [IV]). These clinical studies have indicated that vestipitant is safe and well tolerated at the doses tested. Two studies have specifically supported the use of the current IV formulation of vestipitant for the treatment of breakthrough post-operative nausea and vomiting (PONV).

Phase: II

Study Period: 13 March-2012 to 22 August 2012.

Study Design: Randomized, single-blind, active-controlled, parallel group study with 5 treatment groups receiving vestipitant and 1 treatment group receiving ondansetron.

Centers: Multicenter study: 38 centers in 6 countries (Russia – 12 centers, US – 7 centers, Germany – 6 centers, UK – 5 centers, Poland – 4 centers, and Ukraine – 4 centers).

Indication: Breakthrough PONV.

Treatment: Vestipitant was supplied as an IV solution (2 mg/mL) and administered as an IV infusion at a dose of either 6 mg, 12 mg, 18 mg, 24 mg or 36 mg, for a duration of 30 seconds. The control treatment was an identical volume of ondansetron (2 mg/mL) for injection administered at a dose of 4 mg as a slow IV injection over a period of no less than 30 seconds but preferably between 2 to 5 minutes.

Objectives: The objectives of this study were:

- To evaluate the efficacy, safety, and tolerability of 6 mg, 12 mg, 18 mg, 24 mg, or 36 mg IV doses of vestipitant versus a standard dose of 4 mg ondansetron to treat breakthrough PONV after a failed prophylaxis regimen that included 4 mg IV ondansetron prior to surgery.
- To examine the benefit of IV doses of vestipitant on post-operative symptoms of nausea compared to ondansetron.
- To evaluate the impact of IV doses of vestipitant on discharge readiness and time to discharge compared to ondansetron.
- To evaluate the pharmacokinetic (PK) and exposure-response relationship of IV vestipitant in subjects with PONV.

Statistical Methods:

Efficacy data: The primary efficacy endpoint was based on the number and percent of subjects who achieved Complete Response (CR) defined as no emesis and no further rescue medication from 10 minutes post-infusion end through 24 hours or discharge from the hospital, whichever was sooner. A subject was to be considered as a Treatment Failure if CR was not achieved. Treatment Failure was defined as recurrent emesis more than 10 minutes after Study Treatment was administered or if any antiemetic, including ondansetron, was required for control of nausea/emesis more than 10 minutes after Study Treatment was administered. Time from infusion end to Treatment Failure was to be analyzed using a Cox proportional hazards model including treatment group as a covariate. The date and time when a subject experienced Treatment Failure, along with the primary cause of Treatment Failure were to be listed. Additional evaluations of efficacy included number and percent of subjects having no emesis or retching as well as the average and distribution of Nausea Numeric Rating Scale (NNRS) results. The NNRS was to be assessed once pre-dose, 5, 10, and 15 minutes post-dose, then every 15 minutes through 2 hours post-dose, then every 2 hours (while awake) through 24 hours post-dose or immediately prior to discharge, whichever was sooner. In addition, NNRS was to be assessed once at the time of Follow-up. Emesis was to be assessed once pre-dose then continually through 24 hours post-dose or immediately prior to discharge, whichever was sooner. In addition, emesis was assessed at Follow-up covering the interval since the last post-dose assessment. Time to PONV Discharge-Ready was defined as when, disregarding all other considerations, the subject had no PONV findings that would prevent the subject from being discharged from the hospital/clinic.

Pharmacokinetic data: Pharmacokinetic data were analyzed using noncompartmental analysis methods. All PK concentration data and PK parameter data were listed and summarized. The following PK parameters were calculated using a non-compartmental approach, as appropriate, from the individual plasma concentration profiles collected

following drug administration: Area under the plasma drug concentration-time curve (AUC) from time zero to 1 hour, 6 hours, 24 hours post-dose and the AUC from time zero to the last measurable concentration ($AUC_{0\text{-last}}$), and AUC from time zero to infinity ($AUC_{0\text{-}\infty}$), maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (t_{max}), apparent terminal elimination half-life ($t_{1/2}$) were calculated. In addition, total body clearance (CL) and volume of distribution (V_{ss}) were calculated for vestipitant only. Concentration data was summarized at each nominal timepoint with the following descriptive statistics: sample size (n), mean (Mean), standard deviation (SD), coefficient of variation (CV%), geometric mean (GeoMean), geometric CV% (GeoCV%), median (Median), minimum (Min), maximum (Max). Mean plasma concentrations (+SD) were plotted versus nominal sampling time on linear-linear and log-linear scales. The same scale was to be used for mean plots, when possible. Dose proportionality was also assessed.

Safety data: Summaries of actual values and changes from baseline in the following parameters were produced: adverse events (AEs) and serious adverse event (SAE) observations, vital signs, electrocardiograms (ECGs), and safety laboratory evaluations (hematology, clinical chemistry, and liver chemistry Follow up criteria).

Study Population: Male or female (non-child bearing potential), post-operative surgical subjects, 18 to 75 years of age, with 3 or more independent risk factors for PONV (female gender, non-smoker, history of PONV or motion sickness or planned post-operative opioids), who had received one dose of ondansetron as part of a PONV prophylaxis regimen for the surgical procedure, received general anesthesia and had experienced breakthrough PONV, were eligible to enroll into the study.

Subject Disposition:

Number of Subjects:	Ondansetron 4 mg (N=92)	Vestipitant 6 mg (N=82)	Vestipitant 12 mg (N=93)	Vestipitant 18 mg (N=86)	Vestipitant 24 mg (N=75)	Vestipitant 36 mg (N=99)	Total (N=527)
Treated, n (%)	19 (20.7)	23 (28.0)	24 (25.8)	23 (26.7)	20 (26.7)	22 (22.2)	131(24.9)
Completed, n (%)	18 (94.7)	22 (95.7)	21 (87.5)	21 (91.3)	19 (95.0)	21 (95.5)	122(93.1)
Not Completed, n (%)	1 (5.3)	1 (4.3)	3 (12.5)	2 (8.7)	1 (5.0)	1 (4.5)	9 (6.9)

Demographics (Intention to Treat [ITT] Population):

		Vestipitant					
	Ondansetron 4 mg (N=92)	6 mg (N=82)	12 mg (N=93)	18 mg (N=86)	24 mg (N=75)	36 mg (N=99)	Total (N=527)
Females: Males	19:0	23:0	22:1	21:2	19:1	20:2	124:6
Mean Age in Years (Standard deviation [SD])	44.8 (13.81)	47.4 (11.52)	47.0 (11.22)	45.8 (12.89)	40.9 (13.37)	45.7 (10.25)	45.4 (12.12)
Race							
White, n (%)	17 (89.5)	22 (95.7)	21 (91.3)	22 (95.7)	19 (95.0)	22(100.0)	123(94.6)
Black or African American, n (%)	2 (10.5)	0 (0.0)	2 (8.7)	1 (4.3)	1 (5.0)	0 (0.0)	6 (4.6)
Asian, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Pacific Islander, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other, n (%)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)

Efficacy Results: There were no statistically significant efficacy findings seen in this study. The only vestipitant group which had a lower CR rate than the ondansetron group was the vestipitant 18 mg group with a 1.2% lower CR rate. The vestipitant 6 mg and 24 mg groups, both demonstrated a > 20% improvement from ondansetron, however they did not reach a posterior probability of success > 0.457.

Complete Response Rate (ITT Population):

	Ondansetron 4 mg (N=19)	Vestipitant 6 mg (N=24)	Vestipitant 12 mg (N=23)	Vestipitant 18 mg (N=22)	Vestipitant 24 mg (N=20)	Vestipitant 36 mg (N=22)
Complete Response, n (%)	8 (42.1)	15 (62.5)	12 (52.2)	9 (40.9)	13 (65.0)	13 (59.1)
Improvement from Control (Vestipitant - Ondansetron)%		20.4	10.1	-1.2	22.9	17.0
Posterior Probability of Success		0.222	0.052	0.039	0.065	0.254

Treatment Failure (ITT Population):

	Ondansetron 4 mg (N=19)	Vestipitant 6 mg (N=23)	Vestipitant 12 mg (N=23)	Vestipitant 18 mg (N=23)	Vestipitant 24 mg (N=20)	Vestipitant 36 mg (N=22)	Vestipitant Total (N=111)	Total (N=130)
Treatment Failure (TF), n (%)	11 (57.9)	9 (37.5)	11 (47.8)	13 (59.1)	7 (35.0)	9 (40.9)	49 (44.1)	60 (46.2)
Primary Reason for TF								
Emesis/Retching, n (%)	7 (36.8)	3 (12.5)	1 (4.3)	3 (13.6)	1 (5.0)	2 (9.1)	10 (9.0)	17 (13.1)
Rescue Medication, n (%)	4 (21.1)	6 (25.0)	10 (43.5)	10 (45.5)	6 (30.0)	7 (31.8)	39 (35.1)	43 (33.1)
Emesis/Retching after Rescue Medication, n	1	1	6	2	2	4	15	16

NNRS Summary by Status of Treatment Failure (ITT Population):

	Subjects who had Complete Response		Subjects who had Treatment Failure	
Treatment Group	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Ondansetron 4 mg	7	6.6 (3.31)	10	6.7 (2.83)
Vestipitant 6 mg	15	6.5 (2.53)	9	5.6 (3.54)
Vestipitant 12 mg	11	7.5 (1.81)	11	5.4 (3.72)
Vestipitant 18 mg	8	7.5 (3.16)	11	5.7 (3.82)
Vestipitant 24 mg	13	8.4 (1.33)	7	8.1 (1.57)
Vestipitant 36 mg	13	8.0 (2.80)	8	6.9 (3.04)

Time to PONV Discharge-Ready (ITT Population):

	Ondansetron 4 mg (N=19)	Vestipitant 6 mg (N=24)	Vestipitant 12 mg (N=23)	Vestipitant 18 mg (N=22)	Vestipitant 24 mg (N=20)	Vestipitant 36 mg (N=22)
Median Time to Event (hours)	3.25	1.50	2.13	5.33	3.33	3.05
95% Confidence Interval (CI)	(1.67, 6.82)	(0.80, 1.97)	(1.58, 6.78)	(1.33, 24.00)	(1.03, 28.00)	(0.75, 14.00)
Log-Rank P-value (Vestipitant vs. Ondansetron)		0.1642	0.9686	0.3939	0.2694	0.7493

Time to PONV Discharge Ready (hours) - CR subjects only:

N	8	15	12	7	9	13
Mean (SD)	4.154 (8.2554)	1.015 (0.6721)	2.198 (2.6872)	0.730 (0.6403)	5.562 (9.3837)	3.908 (6.9179)
Median	1.335	1.000	1.755	0.650	1.030	1.270
Min, Max	0.25, 24.43	0.17, 2.02	0.08, 10.00	0.17, 1.80	0.25, 24.00	0.08, 24.08

Time to Treatment Failure (ITT Population):

Median Time to Event (hours)	2.88	NA	NA	10.56	NA	NA
95% CI	(0.48, NA)	(4.07, NA)	(2.55, NA)	(3.20, NA)	(1.47, NA)	(2.38, NA)
Log-Rank P-value (Vestipitant vs. Ondansetron)		0.1323	0.3769	0.5640	0.1275	0.1876

Time to Treatment Failure (hours) - TF subjects only:

N	11	9	11	13	7	9
Mean (SD)	1.443 (1.4621)	3.477 (4.6788)	3.886 (5.9128)	5.527 (5.9780)	1.884 (2.1585)	2.686 (2.5346)
Median	0.570	1.000	1.220	3.400	0.750	2.250
Min, Max	0.17, 4.47	0.38, 11.65	0.17, 19.33	0.85, 21.65	0.25, 6.00	0.42, 7.65

Time to Discharge (ITT Population):

Median Time to Event (hours)	47.72	85.21	95.83	48.47	90.50	74.11
95% CI	(3.42, 144.82)	(45.30, 143.50)	(46.42, 142.75)	(7.15, 93.90)	(4.42, 165.18)	(41.52, 143.70)
Log-Rank P-value (Vestipitant vs. Ondansetron)		0.8343	0.5741	0.6913	0.5038	0.4161

Interim Analysis Results: An interim analysis was performed after the minimum number of CR results was available. The analysis showed that none of the vestipitant doses had a greater than 30% chance of meeting the primary efficacy endpoint. The results met the protocol futility criterion b (< 30% chance of declaring any dose successful, i.e. Pr(pVes > pOn + 0.2 | data) < 0.30) and thus the study was stopped for futility.

PK Results:

Summary of Selected Plasma Vestipitant PK Parameters after Single Dose IV Infusions of Vestipitant, or Ondansetron – Geometric Mean (CV%, n):

PK Parameters	Vestipitant 6 mg (N=24)	Vestipitant 12 mg (N=23)	Vestipitant 18 mg (N=22)	Vestipitant 24 mg (N=20)	Vestipitant 36 mg (N=22)
AUC_{0-1} (ng·hr/mL)	62.8 (129.2, 16)	75.7 (87.2, 17)	103 (103.3, 17)	138 (265.9, 16)	276 (58.3, 18)
AUC_{0-6} (ng·hr/mL)	188 (71.0, 15)	219 (40.2, 14)	361 (37.6, 11)	495 (115.5, 12)	824 (37.3, 18)
AUC_{0-24} (ng·hr/mL)	291 (47.4, 14)	433 (27.0, 12)	773 (34.8, 10)	1106 (45.3, 11)	1626 (35.3, 15)
AUC_{last} (ng·h/mL)	245 (113.3, 16)	307 (92.6, 17)	351 (211.6, 17)	623 (132.0, 16)	1393 (42.1, 18)
AUC_{∞} (ng·h/mL)	308 (38.1, 11)	515 (27.5, 8)	789 (47.7, 5)	1221 (32.5, 5)	1354 (55.1, 4)
C_{max} (ng/mL)	205 (305.7, 16)	204 (174.4, 17)	331 (150.8, 17)	423 (211.3, 16)	809 (123.5, 18)
t_{max}[a] (hr)	0.05 (0.03-0.08, 16)	0.05 (0.03-0.27, 17)	0.07 (0.03-1.00, 17)	0.05 (0.03-6.00, 16)	0.05 (0.03-0.27, 18)
$t_{1/2}$ (hr)	7.71 (20.2,11)	7.72 (20.5, 8)	9.69 (5.5, 5)	5.76 (40.2, 5)	6.79 (27.3, 4)
CL (L/hr)	19.5 (38.1, 11)	23.3 (27.5, 8)	22.8 (47.7, 5)	19.6 (32.5, 5)	26.6 (55.1, 4)
V_{ss} (L)	172 (93.3, 13)	261 (33.0, 11)	274 (28.0, 8)	189 (81.6, 9)	248 (39.8, 13)

[a] Median (Min – Max, Sample Size).

Summary of the Power Model Analysis of Plasma Vestipitant PK Parameters

C_{max}	0.776 (0.345, 1.208)
AUC_{0-24}	0.994 (0.846, 1.142)
AUC_{∞}	0.888 (0.684, 1.093)

Safety Results: AEs and SAEs were collected starting at Dosing (0 hours) and continued through the Follow-up visit.

Adverse Events (Safety Population)

	Ondansetron 4 mg (N=19)		Vestipitant 6 mg (N=23)		12 mg (N=24)		18 mg (N=23)		24 mg (N=20)		36 mg (N=22)		Total (N=131)	
		Subjects		Subjects		Subjects		Subjects		Subjects		Subjects		Subjects
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
All AEs	16	9 (47.4)	18	10 (43.5)	20	13 (54.2)	27	12 (52.2)	15	10 (50.0)	21	12 (54.5)	117	66 (50.4)
Related AEs	0	0 (0.0)	0	0 (0.0)	2	1 (4.2)	5	3 (13.0)	4	2 (10.0)	1	1 (4.5)	12	7 (5.3)
SAEs	0	0 (0.0)	1	1 (4.3)	1	1 (4.2)	4	2 (8.7)	0	0 (0.0)	1	1 (4.5)	7	5 (3.8)

There were no deaths and no AEs leading to withdrawal from the study.

As can be anticipated for this population of post-surgical subjects, the most common AE reported was procedural pain. This was highest in the vestipitant 36 mg group (36.4%) and lowest in the vestipitant 18 mg group (8.7%).

There were clear infusion site observations during this study. Procedural and site administration pain and discomfort were reported in 26.7% of subjects overall. The most common procedural and site administration pain and discomfort AEs were procedural pain (21.4%), injection site pain (2.3%) and pain (1.5%). Application site pain was reported in 1 subject (4.5%) in the vestipitant 36 mg group. Injection site pain was reported in 2 subjects (8.3%) in the vestipitant 12 mg group and 1 subject (5.0%) in the vestipitant 24 mg group. Injection site paresthesia was reported in 1 subject (4.5%) in the vestipitant 36 mg group. In addition, pain was reported in 1 subject (5.3%) in the ondansetron group, and 1 subject (5.0%) in the vestipitant 24 mg group.

There were 12 AEs reported for 7 subjects that were considered to be related to the investigational product. No related AEs were reported for the ondansetron or vestipitant 6 mg groups. There were 2 related AEs (injection site pain and edema peripheral) reported in the vestipitant 12 mg group, 5 related AEs reported for 3 subjects in the vestipitant 18 mg group (dizziness, alanine aminotransferase increased, aspartate aminotransferase increased, and gamma-glutamyl transpeptidase increased), 4 related AEs reported for 2 subjects (injection site pain, dysgeusia, blood pressure increased and heart rate increased) in the vestipitant 24 mg group and 1 related AE (application site pain) reported in the vestipitant 36 mg group.

There were 4 SAEs reported in 2 subjects in the vestipitant 18 mg group, there were no SAEs reported for more than 1 subject in any other treatment group. In addition, there were no SAEs reported for subjects in the ondansetron group or the vestipitant 24 mg group.

Clinical Laboratory Evaluations: There were no clinically significant mean changes from baseline in any laboratory parameter during the course of the study. There were no laboratory changes over time of note and there were no individual subject changes in hematology or serum chemistry variables of note at any time point. No liver events were reported during this study

Conclusion:

There were no statistically significant efficacy findings seen in this study. The vestipitant 6 mg and 24 mg groups, both demonstrated a > 20% improvement from ondansetron, however they did not reach a posterior probability of success > 0.457.

An interim analysis showed that none of the vestipitant doses had a greater than 30% chance of meeting the primary efficacy endpoint (superiority defined as finding the lowest dose of vestipitant that exceeds the performance of ondansetron by 20%). The results met the protocol futility criterion b (< 30% chance of declaring any dose successful, i.e. Pr(pVes > pOn + 0.2 | data) < 0.30) and thus the study was stopped for futility.

There were no deaths and no AEs leading to withdrawal from the study. The most common AE reported was procedural pain.

There was no significant pattern observed for any ECG changes; as all time points were relatively close to the baseline, the changes seen are expected for this post-surgical population during the recovery period.

There was no significant pattern observed for any vital sign changes; as all time points were relatively close to the baseline, the changes seen are expected for this post-surgical population during the recovery period.

There were no clinically significant mean changes from baseline in any laboratory parameter during the course of the study. There were no laboratory changes over time of note and there were no individual subject changes in hematology or serum chemistry variables of note at any time point. No liver events were reported during this study