

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-198

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA:	22-198
Brand Name:	Sancuso
Generic Name:	Granisetron
Dosage form and Strength:	Transdermal delivery system (TDS) 52 cm ² (34.3 mg) patch
Route of administration:	Transdermal
Proposed Indication:	For the prevention of nausea and vomiting in patients receiving up to 5 consecutive days of moderately and/or highly emetogenic chemotherapy.
Sponsor:	Strakan Pharmaceuticals Limited
Type of submission:	Original Submission [505(b)(2)]
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCP Division:	DCP III
Priority:	Standard
Submission date:	06/29/07, 03/05/08, 03/06/08, 05/05/08
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

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1. Executive Summary

1.1 Recommendations

NDA 22-198 for Sancuso (granisetron transdermal delivery system; GTDS) has been reviewed by the Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III). From the OCP standpoint, the clinical pharmacology section of the NDA is acceptable. The labeling comments on p. 17 should be communicated to the Medical Officer and sponsor.

1.2 Phase IV Commitments:

1. Based on the data submitted, it appears that a significant subcutaneous fat store exists with the use of this patch. Therefore, the sponsor should commit to undertake an *in vivo* PK study in subjects with differing levels of body fat (and thus subcutaneous fat) composition.
2. Heat has been shown to markedly increase the rate of drug absorption into the systemic circulation from transdermal dosage forms. Given that this product is intended for multi-day use, the sponsor should commit to conduct an *in vivo* PK study to determine the impact of heat on drug delivery.

The details of these phase 4 commitments are under discussion.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Chemotherapy-induced nausea and vomiting (CINV) has long been recognized as a treatment side effect. Agents with the highest emetogenic potential result in emesis during the first 24 hours post-chemotherapy in most of patients without anti-emetic prophylaxis. Patients can experience nausea and vomiting minutes to hours after chemotherapy is administered.

One of the mechanisms involved in CINV is the release of serotonin from mucosal enterochromaffin cells, which stimulates 5-HT₃ receptors. This evokes vagal afferent discharge, inducing vomiting. Granisetron is a 5-HT₃ antagonist. Roche's Kytril (granisetron HCl) 1 mg oral tablets, oral solution (2 mg base/10 mL) and Injection (0.1 mg base/mL; 1 mg base/mL; and 4 mg base/4 mL) have been approved for prevention of CINV.

On 06/29/07, Strakan submitted the Sancuso NDA seeking approval for GTDS 52 cm² patch for prevention of CINV, the subject of this Clinical Pharmacology review. It was filed under 505 (b)(2) referencing Kytril oral tablets.

Formulation

During the clinical development of GTDS, the manufacturer of the patch changed from _____ to Aveva DDS Inc. while there was no change in the formulation. Granisetron patch manufactured by _____ was used in 2 Phase 1 PK studies, 392MD/4/C and 392MD/11/C and in a Phase 2 clinical trial, 392MD/8/C. The Aveva produced patch was used in the Phase 1 Sensitization and Irritation study (392MD/26/C) and the Phase 3 clinical study (392MD/15/C). Sancuso patches made at these two manufacturing sites showed comparable plasma profiles.

b(4)

Overview

Five clinical studies were submitted to support the NDA as shown in Table 1. All the 5 studies had PK information.

Table 1. Overview of Clinical Studies for Sancuso, Granisetron TDS, Patch

Study No.	Phase	Patient Population/ No.	Patch Manufacturer	Design/Dosage/Site/Duration of Application
392MD/4/C	I	Healthy Subj 6 M & 6 F.	Old	Single 5-day application of the active patch GTDS; 15cm ² (9.9 mg) on abdomen for 5 days
392MD/11/C	I	Healthy Subj 12 M Subj.	Old	4x4 XO; single 6-day application per treatment 1. GTDS: 15cm ² (9.9mg), 33 cm ² (21.8mg), 52cm ² (34.3mg) on upper arm for 6 days 2. Oral granisetron tablets 2mg QD x 5 days
392MD/8/C	II	63 M & 110 F Patients receiving single-day Moderate Emetogenic Chemo.	Old	Randomized, double-blind, parallel group study (patch: single 5-day application) 1. GTDS: 52cm ² (34.3mg) on upper arm for 5 days + oral Pbo for one day 2. Pbo patch for 5 days + oral G. 2 x 1mg tab for one day.
392MD/15/C	III	318 M & 323 F Patients receiving Moderately or Highly Emetogenic multiple-day Chemo.	New (Scale-up Production)	Randomized, double-blind, parallel group study (patch: single 7-day application) 1. GTDS: 52cm ² (34.3mg) on upper arm for 7 days + oral Pbo 2. Pbo patch x 7 days +oral G. 2 x 1mg tab. (3-5 days)
392MD/26/C	I	Healthy Subj 54 M & 158 F	New (Scale-up Production)	Randomized, double-blind, parallel group, multiple patch applications (1 active and 1 Pbo patches on Days 1, 8 and 15) GTDS: one 52cm ² (34.3mg) patch + one Pbo patch on upper arms x 7 days for a total of 3 patches each in 21 days (Note: GTDS: 1 x 52cm ² + 1 Pbo patch on the back x 2 days was also studied.)

*. Pbo= placebo; tab.= tablet.
Patch manufacturer: old _____ ; new (Aveva DDS) for scale-up production.

b(4)

Note:

A study on possible metabolites post oral administration and patch application was carried out. Since this study was exploratory in nature, no detailed review was conducted.

Selection of Patch Size and Timing of Patch Application (Relative to Chemotherapy)

The pharmacokinetics of granisetron for three patch sizes and an oral regimen (2 mg QD for 5 days) were evaluated in a 4-way crossover study (Study 392MD/11/C). Mean PK parameters for the granisetron patches obtained from this study were presented in Table 2.

Table 2. Mean (%CV) Granisetron PK Parameters for Three Patch Sizes and Oral Granisetron

Parameter	Study 392MD/11/C				
	15	33	52	Oral QD Dosing x 5 days	
Patch Size, cm ²	15	33	52	Oral QD Dosing x 5 days	
Nominal Dose, mg	9.9	21.8	34.3	2 (per day)	
C _{max} , ng/mL	1.15 (73)	2.08 (110)	3.85 (77)	5.25 (42%) (Day 1)	5.50 (68%) (Day 5)
T _{max} , hr ¹	48 [48-96]	48 [24-150]	48 [24-168]	1.5 [1-4]	2 [1-4]
T _{1/2} , hr	30.9 (32)	30.9 (21)	35.9 (35)	6.4 (74%)	7.9 (74%)
AUC _{0-t} , ng-hr/mL ²	98 (83%)	179 (110%)	321 (89%)	51 (80%)	62 (110%)
C _{avg} , ng/mL ³	0.68 (83%)	1.24 (110%)	2.23 (89%)	2.14 (79%)	2.60 (108%)

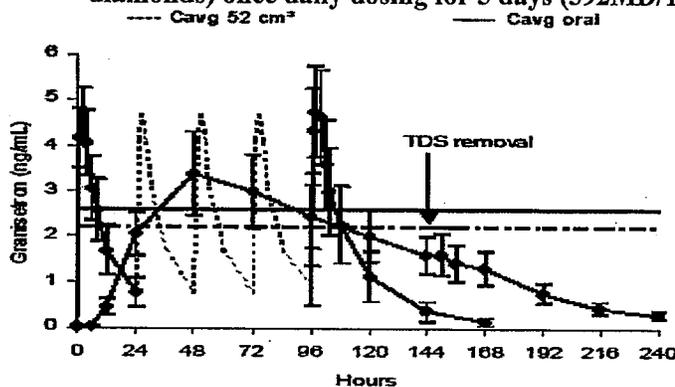
¹ Median [range].

² AUC_{0-t}: AUC₀₋₁₄₄ for patch application for 6 days and AUC₀₋₂₄ for QD oral dosing.

³ C_{avg} was calculated as (AUC₀₋₁₄₄)/144 hr for patch application and (AUC₀₋₂₄)/24 hr for oral dosing.

The mean C_{avg} level (2.23 ng/mL over 144 hrs postdose) for the 52 cm² GTDS patch is within the mean C_{avg} values of 2.14 ng/mL (Day 1) and 2.60 ng/mL (Day 5) following an oral administration of 2 mg/day for 5 days (also shown in Figure 1 below). The GTDS 52 cm² patch was therefore selected by the sponsor for further development.

Figure 1. Mean (± SEM) plasma granisetron concentration-time profiles for the 52cm² granisetron TDS (filled diamonds) and 2 mg oral granisetron (open diamonds) once daily dosing for 5 days (392MD/11/C)

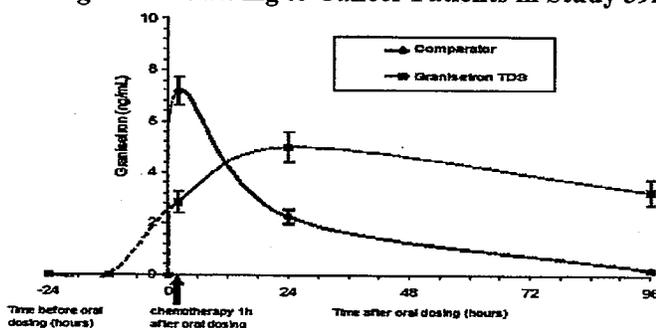


The GTDS 52 cm² patch was further tested in a Phase 2 Study 392MD/8/C. This was a study in 173 patients undergoing a single-day regimen of chemotherapy with moderately emetogenic (ME) potential. A 5-day patch application (starting on Day -1) was compared with a single oral dose of 2 mg tablet. The mean (±SEM) granisetron plasma concentration-time data are shown in

Figure 1. High intersubject variability was observed for both the patch (CV >100%) and oral granisetron tablets (CV: 80% to >100%).

Based on the results from Study 392MD/8/C, the 52 cm² patch was considered the appropriate size for the Phase 3 Study. Further, due to the lower initial concentrations observed with the patch (Figure 2) and lower control of nausea and vomiting during the initial 0-24 hr of chemotherapy when compared to oral granisetron, the patch was therefore proposed to be applied onto the upper outer arm 24 to 48 hrs before the start of chemotherapy in the Phase 3 trial 392MD/15/C.

Figure 2. Mean (\pm SEM) Plasma Granisetron Concentrations following 5-day application of Granisetron TDS and single Oral Administration of granisetron 2 mg to Cancer Patients in Study 392MD/8/C (fitted curves)



PK Characteristics for Granisetron TDS

PK results from Study 392MD/26/C was presented here as this study used the patch manufactured at the proposed commercial site. This study was conducted to evaluate the sensitization and irritation of GTDS patch in healthy volunteers. A subset of 24 subjects (12 females & 12 males) had blood samples taken for PK analysis after the first patch application.

The plasma granisetron concentration-time profiles following single 7-day application of GTDS patch are shown in Figure 3 and their mean PK parameters for GTDS patch are presented in Table 3-1. Plasma granisetron concentration peaked at approximately 72 hours (mean; range: 24-168 hrs) following patch application. (Note: The T_{max} estimate was limited by the sampling scheme.) At 168 hours following patch application, mean plasma granisetron concentration declined to approximately half of the mean C_{max} value. Intersubject variability in both C_{max} and AUC was very high (CV: ~170%).

Figure 3. Mean (\pm SD) Granisetron Plasma Profiles in Healthy Male (n = 12) and Female subjects (n=12); Study 392MD/26/C

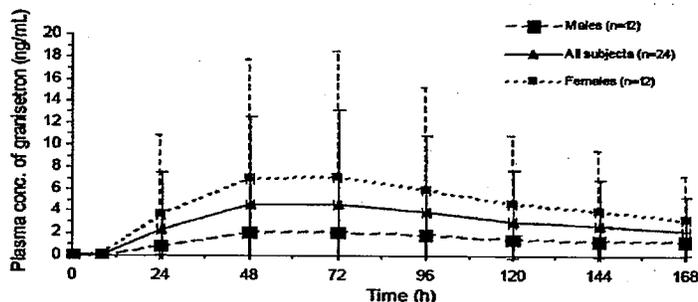


Table 3-1. Mean (CV%) Granisetron PK Parameters in Healthy Male (n=12) and Female Subjects (n = 12) in Study 392MD/26/C

PK Parameters	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₁₆₈ (ng-hr/mL)	C _{avg} (ng/mL)
All Subjects	5.0 (170)	72 [24-168] ¹	527 (173)	3.1 (170)
Male (n=12)	2.5 (110)	66 [24-144]	253 (115)	1.5 (120)
Female (n=12)	7.6 (150)	78 [24-168]	802 (150)	4.8 (150)

¹. Mean [Range].

Gender Difference

PK: Gender differences for granisetron plasma data were observed in study 392MD/26/C (Figure 3 & Table 3-1). Female subjects were found to have a 3-fold higher systemic exposure than male subjects. One female subject (#23) had unusually high (8-fold of female mean value) plasma granisetron levels after GTDS application. The reason for this observation is unknown. When Subject #23 is excluded from the analysis, female subjects still had 80% higher mean C_{max} and AUC compared to male subjects (Table 3-2).

Table 3-2. Mean (CV%) Granisetron PK Parameters in Healthy Male (n=12) and Female Subjects (n = 11); Study 392MD/26/C

PK Parameters	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₁₆₈ (ng-hr/mL)	C _{avg} (ng/mL)
All Subjects ¹	3.4 (79)	72 [24-168] ²	351 (85)	2.1 (170)
Male (n=12)	2.5 (110)	66 [24-144]	253 (115)	1.5 (120)
Female (n=11)	4.4 (55)	79 [24-168]	459 (60)	2.7 (150)

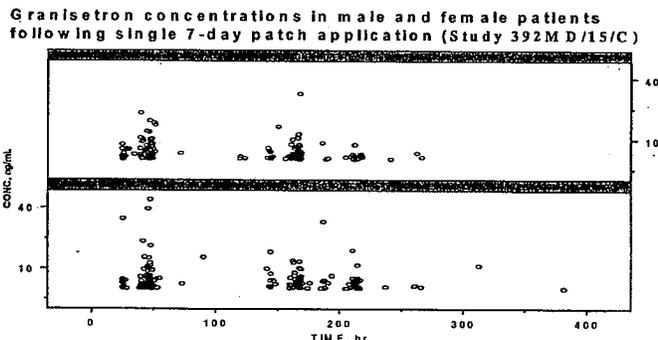
¹. Excluding female subject # 23.

². Mean [Range].

Additional analysis was performed for granisetron plasma levels obtained from the pivotal Phase 3 study 392MD/15/C. This was a non-inferiority study in 641 patients receiving ME and/or highly emetogenic (HE) multi-day chemotherapy. Patients were randomized in a 1:1 ratio for GTDS 52 cm² patch (from Aveva DDS) and the active comparator, oral granisetron. Limited blood sampling for granisetron levels was available on Day1 (1 hr post capsule ingestion, i.e., immediately before start of chemotherapy) and at 24 hrs postdose of last day chemotherapy.

Upon our request, the sponsor provided scatter plots to compare the granisetron concentrations in males (upper panel; in purple) and females (lower panel; in blue) (Figure 4). Although more

female patients had high concentrations (>30 ng/mL), generally the concentration range was similar between males and females.



Clinical efficacy outcome: The following information was obtained from Dr. Karyn Berry of the Division of Gastroenterology Products.

In the pivotal study, 392MD/15/C, the primary efficacy endpoint, “complete control” was defined as no vomiting or retching, no more than mild nausea, and no rescue medication from the first administration until 24 hours after the start of administration of the multiday chemotherapy. There was no significant difference in % responders between male and female subpopulations. In fact, numerically, male patients had a higher response rate (64.2%) than female patients (56.5%).

Note: A mean of 40.6 (\pm 9.9) hrs [range: 25.5 to 72.3 hr] of lapse time for active patch (n=307) and that for placebo patch (n=314) was 40.4 (\pm 9.5) hr [range: 24.5 to 68.7 hr].

Reviewer’s Comment:

There is evidence to suggest that female subjects had higher granisetron concentrations following patch application. Based on the Phase 3 trial results, it appears that any gender differences in PK did not translate into clinical efficacy outcome.

Rate of Drug Delivery from Granisetron Patch

The released dose was calculated as the applied dose (initial drug content in the patch) minus the residual granisetron amount in the patch after removal. The sponsor then defined the mean “*in vitro* flux” as the mean released dose per day, which was calculated as the released dose divided by the days of patch application (5, 6, or 7 days). Based on Study 392MD/26/C, mean “*in vitro* flux” was estimated to be 3.10 mg/day (CV: 16.6%).

Reviewer’s comment:

Using the term “*in vitro* flux” can be misleading as it implies that the value was obtained from an *in vitro* study and that the drug release rate from the patch was relatively constant over the intended time period of use (whereas after GTDS patch application, plasma granisetron level actually varied with time lapse). We will consider it as the average daily delivery rate.

It appears that the drug, after permeating through the skin, can be stored in the subcutaneous adipose tissue first and subsequently released to systemic circulation.

Safety and efficacy

The following information was obtained from Dr. Karyn Berry of the Division of Gastroenterology Products.

The results of assessment of patch adhesion obtained from the Phase 3 pivotal study 392MD/15/C indicated acceptable patch adhesiveness for the overall study period. Two thirds of the patients had at least 90% patch adhesion and 90% of the patients in the GTDS group had \geq 75% adhesion of the total patch area and < 1% of patients had patches detached. Additionally, adhesion was related to clinical outcome.

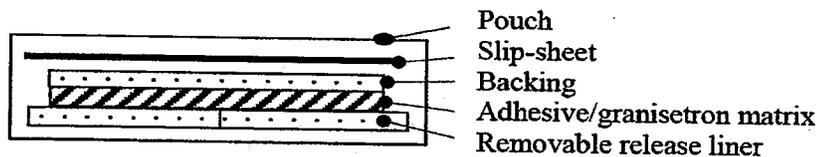
The pivotal Phase 3 study showed that for the acute-phase CINV (0-24 hrs), the % responders was comparable between the GTDS (60.2 %) and oral granisetron (64.8 %) groups. The overall incidence of treatment emergent adverse events (TEAEs) and related TEAEs were comparable between the transdermal and oral groups. For Sancuso GTDS patch, the most common adverse event is constipation which had a slightly higher rate (8.7%) than that of oral dosing (4.9%). Other adverse events are comparable between GTDS and oral dosing.

2. Question Based Review

2.1 General Attributes

Formulation:

Granisetron base was used as the drug substance rather than granisetron hydrochloride, as the non-ionized material is the form most likely to provide acceptable skin permeation properties. Granisetron transdermal delivery system (referred to as GTDS) is a dermal patch formulation. The patch consists of a matrix of granisetron base in a commercially-available adhesive, _____ as shown below:



The _____ is an _____ adhesive. _____

Sancuso GTDS is a 52 cm² patch containing a nominal dose of 34.3 mg of granisetron. The formulation was designed to deliver granisetron for up to 7 days following dermal application in order to increase patient compliance during chemotherapy.

Mechanism of Action:

In general, vomiting triggered by drugs or chemical agents is mediated through the CTZ (chemoreceptor trigger zone). The mode of action of granisetron is believed to be through binding to 5-HT₃ receptors, blocking serotonin stimulation, and thus preventing vomiting in response to emetogenic stimuli such as chemotherapy.

Indication:

Sancuso GTDS patch is indicated for the prevention of nausea and vomiting in patients receiving up to 5 consecutive days of moderately and/or highly emetogenic (ME and/or HE) chemotherapy.

Proposed Dosing Regimen:

For adults, apply a single patch to the upper outer arm 24-48 hours before chemotherapy as appropriate and remove the patch a minimum of 24 hours after completion of chemotherapy. The patch can be worn for a minimum of 24 hrs after completion of chemotherapy and up to 7 days depending on the duration of the chemotherapy regimen.

2.2 General Clinical Pharmacology

Q1. How was the Sancuso Patch Size (52 cm²) Selected?

The patch size selection was primarily based on the Phase 1 Study 392MD/11/C. This was a four-way crossover study in 12 healthy male subjects to assess the bioavailability of three sizes of granisetron patches (15, 33 and 52 cm²) following a single 6-day application and an oral granisetron regimen (2 mg once-daily for 5 days).

The mean plasma granisetron concentration-time profiles for the 3 sizes (15 cm², 33 cm², and 52 cm²) of Sancuso GTDS after being applied on the upper outer arm for 6 days are shown in Figure 5 and the mean granisetron PK parameters for the 3 patch sizes and for oral dosing are presented in Table 4.

Figure 5. Mean (± SEM) plasma granisetron concentration versus time after application of one GTDS patch (15, 33, and 52 cm²) on the upper outer arm for 6 days to healthy male subjects (n=12)

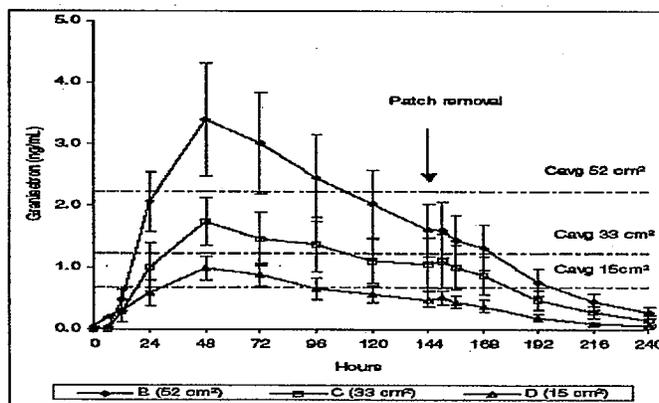


Table 4. Mean Granisetron PK Data Obtained from 12 Healthy Male Subjects

Mean Parameters (CV%)	Study 392MD/11/C				
	15	33	52	Oral QD Dosing x 5 days	
Patch Size, cm ²	15	33	52		
Nominal Dose, mg	9.9	21.8	34.3	2	
C _{max} , ng/mL	1.15 (73)	2.08 (110)	3.85 (77)	5.25 (42%) (Day 1)	5.50 (68%) (Day 5)
T _{max} , hr ¹	48 [48-96]	48 [24-150]	48 [24-168]	1.5 [1-4]	2 [1-4]
T _{1/2} , hr	30.9 (32)	30.9 (21)	35.9 (35)	6.4 (74%)	7.9 (74%)
AUC _{0-t} , ng-hr/mL ²	98 (83%)	179 (110%)	321 (89%)	51 (80%)	62 (110%)
C _{avg} , ng/mL ³	0.68 (83%)	1.24 (110%)	2.23 (89%)	2.14 (79%)	2.60 (108%)

¹ Median [range].

² AUC_{0-t}: AUC₀₋₁₄₄ for patch application for 6 days and AUC₀₋₂₄ for QD oral dosing.

³ C_{avg} was calculated as (AUC₀₋₁₄₄)/144 hr for patch application and (AUC₀₋₂₄)/24 hr for oral dosing.

After repeated 2 mg QD oral dosing, the mean C_{max} was 5.25 ng/mL on Day 1 and 5.50 ng/mL on Day 5, and mean T_{max} was around 1.5-2 hrs. Following GTDS patch application, mean plasma granisetron concentrations peaked at approximately 48 hours (T_{max}, a median) and then declined steadily thereafter even though the patch was still left on the skin. The mean C_{max} for the three patch sizes were 1.15, 2.08, and 3.85 ng/mL, respectively, which were all lower than that observed with oral granisetron 2 mg QD. The mean apparent terminal half-life (T_{1/2}) of granisetron after GTDS patch removal was estimated to be around 31-36 hrs across the patches tested, which was much longer than that observed with oral granisetron (6.5-8.0 hrs). This is likely to be due to the continued drug release from the skin after the patch removal.

The patch size selection was based on the mean C_{avg} value (average plasma concentration). For the patches, C_{avg} was calculated as (AUC₀₋₁₄₄)/0-144 hr which were 0.68, 1.24, and 2.23 ng/mL for the 15, 33, and 52 cm² patches, respectively. For the oral 2 mg QD dosing, C_{avg} was calculated as (AUC₀₋₂₄)/0-24 hr and was evaluated to be 2.14 ng/mL on Day 1 and 2.60 ng/mL on Day 5 (Table 4). As shown in Table 4, C_{avg} (mean: 2.23 ng/mL) for the 52 cm² patch was similar to those obtained from the approved once-daily oral dosing of 2 mg granisetron (Day1: 2.14 ng/mL and Day5: 2.60 ng/mL). The C_{avg} for the 15 and 33 cm² patches were 0.68 and 1.24 ng/mL, respectively, which were too low compared to that for the oral dosing. The 52 cm² GTDS patch was therefore selected by the sponsor for further development.

Q2. Why Sancuso Patch is proposed to be applied 24-48 hours prior to chemotherapy?

The 52 cm² GTDS patch was tested in a Phase 2 Study 392MD/8/C. This was a study in 173 patients undergoing a single-day regimen of chemotherapy with moderately emetogenic (ME) potential. A 5-day patch application (starting on Day -1) was compared with a single oral dose of 2 mg tablet. Post chemotherapy, blood samples were taken from all patients on Day 0 (1st hr), Day 1 (24th hr) and Day 4 (96th hr). The PK results obtained from the study are shown below:

Figure 6. Mean (\pm SEM) Plasma Granisetron Concentrations following Granisetron TDS and Oral Administration to Cancer Patients in Study 392MD/8/C (along with the fitted curve)

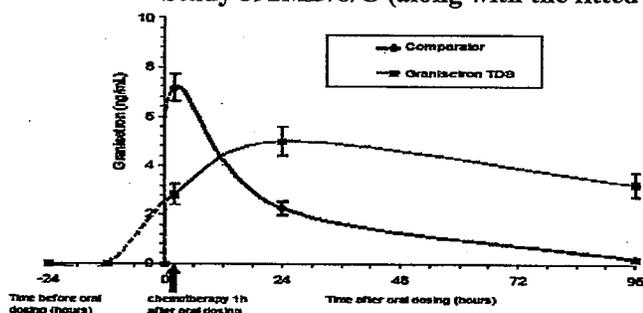


Table 5. Plasma Granisetron Concentrations (ng/mL) following Granisetron TDS and Oral Administration to Cancer Patients in Study 392MD/8/C

Parameter	Study Days				
	Day 0 (1 st hr) [#]	Day 1 (24 h)	Day 4 (96 h)	Day 5 (120 h)	Day 6 (144 h)
Granisetron TDS 52 cm² Patch					
N	86	85	79	10*	10*
Mean \pm SD	2.84 \pm 3.86	5.00 \pm 5.32	3.26 \pm 4.35	0.98 \pm 0.87	0.49 \pm 0.47
Oral Granisetron 2 x 1 mg Tablets					
N	82	81	80	7*	7*
Mean \pm SD	7.17 \pm 4.90	2.28 \pm 2.38	0.19 \pm 0.44	0.04 \pm 0.07	<LOQ

[#] Blood samples taken 1 hr post chemotherapy, i.e., 2 hrs after granisetron oral dosing.

* From a subset of patients.

In patients treated with a single 2 mg dose of oral granisetron (given 1 hr prior to chemotherapy), the mean plasma granisetron value was 7.17 ng/mL at 2 hrs post oral dosing (near its T_{max}). In patients receiving GTDS, mean concentration at this time point (equivalent to 25 hr post patch application) was 2.84 ng/mL and the concentration was higher at 24 hrs after chemotherapy, i.e., 48 hr after patch application (mean: 5.00 ng/mL). Note that high intersubject variability was observed for both the patch (>100%) and oral granisetron tablets (70% to >100%).

The efficacy outcome was measured by the percentage of patients with total control, which was defined as “no vomiting or retching, no nausea, or no rescue medication.” For the delayed CINV, the response rate for the patch was comparable with, but not superior to the oral granisetron (32.2% vs. 29.8%). For the acute CINV, the % responders was lower for the patch compared to oral granisetron (43.7% vs. 52.4%) as shown in Table 6. Since the patch had low initial (0-24 hr) granisetron concentrations, this might explain its lower response rate for the acute CINV. As it might take 48 hours to reach C_{max} , the sponsor proposed to have the patch applied onto the upper outer arm 24 to 48 hrs before the start of chemotherapy in the Phase 3 trial 392MD/15/C.

Table 6: Clinical Outcome from Phase 2 Study 392MD/8/C

Endpoint Total Control:		Number (%) of Patients (ITT)		
		GTDS (n=87)	Oral G (n=84)	Total (n=171)
CINV				
1°:Delayed Phase (24-120 hr)	No	59 (67.8%)	59 (70.2%)	118 (69.0%)
	Yes	28 (32.2%)	25 (29.8%)	53 (31.0%); p=0.6288
2°: Acute Phase (0-24 hrs)	No	49 (56.3%)	40 (47.6%)	89 (52.0%)
	Yes	38 (43.7%)	44 (52.4%)	82 (48.0%); p=0.2445
2°: Overall (0-120 hrs)	No	65 (74.7%)	63 (75.0%)	128 (74.9%)
	Yes	22 (25.3%)	21 (25.0%)	43 (25.1%); p=0.9111

Q3. What are the PK Characteristics of Granisetron After GTDS Application?

The PK data presented below were obtained from Study 392MD/26/C, a study to evaluate the sensitization and irritation of GTDS patch in healthy volunteers, because this study used the 52 cm² patch manufactured at the new site (Aveva DDS). In this study, both the active and placebo patches were simultaneously applied to the upper outer arm on opposite arms on Days 1, 8, and 15. Patches remained in place for 7 days after each application. A subset of 24 subjects (12 females & 12 males) had blood samples taken for PK analysis at predose and at 8, 24, 48, 72, 96, 120, 144, and 168 hrs after the first patch application.

The plasma concentration-time profiles following single 7-day application of GTDS 52 cm² patch are shown in Figure 7-1. The mean PK parameters for GTDS are presented in Table 7-1. Peak plasma concentrations (mean: 5.0 ng/mL) was reached approximately 72 hours following patch application. Plasma concentrations then decline with time even though the patch remained on the skin. At 168 hours following patch application, mean plasma granisetron concentration was approximately half of the mean C_{max} value. Intersubject variability in both C_{max} and AUC was very high (CV: ~170%; Table 7-1).

Figure 7-1. Mean (± SD) Granisetron Plasma Profiles in 24 Healthy Volunteers ; Study 392MD/26/C

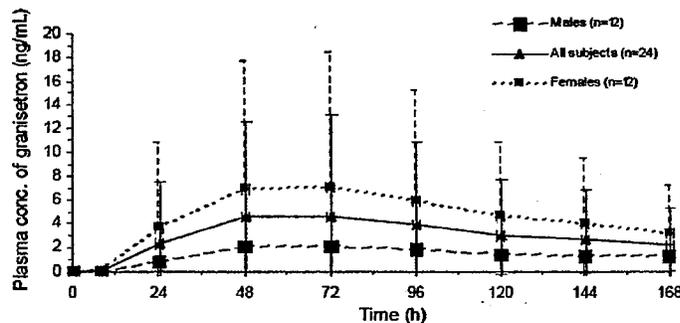


Table 7-1. Mean (CV%) Granisetron PK Parameters in Healthy Volunteers in Study 392MD/26/C

PK Parameters	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₁₆₈ (ng-hr/mL)	C _{avg} (ng/mL)
All Subjects	5.0 (170)	72[24-168] ¹	527 (173)	3.1 (170)
Male (n=12)	2.5 (110)	66 [24-144]	253 (115)	1.5 (120)
Female (n=12)	7.6 (150)	78 [24-168]	802 (150)	4.8 (150)

¹. Mean [Range].

Q4. Are There Gender Differences in Granisetron PK and Efficacy Outcome Following Patch Application?

Pharmacokinetics:

Gender differences for granisetron plasma data were observed in Study 392MD/26/C (Figure 7-1 & Table 7-1). Female subjects were found to have a 3-fold higher systemic exposure than male subjects. One female subject (#23) had unusually high (8-fold of female mean value) plasma granisetron levels after GTDS application. The reason for this observation is unknown. (The sponsor verified that this female subject received only one active patch, the residual amount of granisetron after patch removal was in the same range as those observed for the other subjects (9.9 mg vs. 4.3–16.9 mg), and that the assay method was valid.) When Subject #23 is excluded from the analysis, female subjects still had 80% higher mean C_{max} and AUC compared to male subjects (Table 7-2 and Figure 7-2).

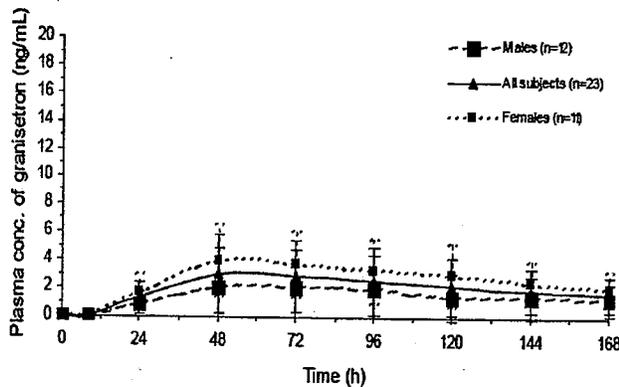
Table 7-2. Mean (CV%) Granisetron PK Parameters in Healthy Male (n=12) and Female Subjects (n = 11); Study 392MD/26/C

PK Parameters	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₁₆₈ (ng-hr/mL)	C _{avg} (ng/mL)
All Subjects ¹	3.4 (79)	72 [24-168] ²	351 (85)	2.1 (170)
Male (n=12)	2.5 (110)	66 [24-144]	253 (115)	1.5 (120)
Female (n=11)	4.4 (55)	79 [24-168]	459 (60)	2.7 (150)

¹. Excluding female subject # 23.

². Mean [Range].

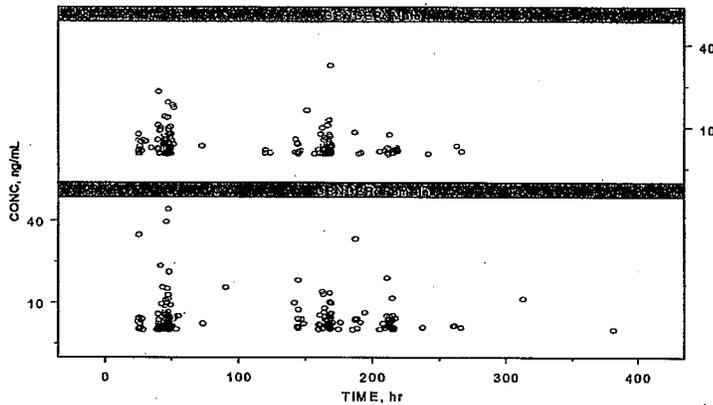
Figure 7-2. Mean (± SD) Granisetron Plasma Profiles in Healthy Male (n = 12) and Female subjects (n=11, excluding Subject #23); Study 392MD/26/C



Additional Analysis:

From the pivotal Phase 3 study, 392MD/15/C, the sponsor provided scatter plots upon our request to compare the granisetron concentrations in males (upper panel; in purple) and females (lower panel; in blue) upon our request (Figure 8 below). Although more female patients had higher concentrations, generally the concentration range was similar between males and females.

Granisetron concentrations in male and female patients following single 7-day patch application (Study 392MD/15/C)



Efficacy outcome:

The following information was obtained from Dr. Karen Berry of the Division of Gastroenterology Products. In the pivotal study, 392MD/15/C, the primary efficacy endpoint, “complete control” was defined as no vomiting or retching, no more than mild nausea, and no rescue medication from the first administration until 24 hours after the start of administration of the multiday chemotherapy. There was no significant difference in % responders between male and female subpopulations. In fact, numerically, male patients had a higher response rate (64.2%) than female patients (56.5%) and this was also true for oral granisetron group (male: 72.4%; female: 57.5%).

Reviewer’s Comment:

There is evidence to suggest that female subjects had higher granisetron concentrations than male subjects following patch application. Based on the Phase 3 trial results, it appears that any gender differences in PK did not translate into differences in clinical efficacy outcome.

Q4. What is the Drug Delivery Rate following Application of Granisetron Patch?

The sponsor defined a term “*in vitro* flux” which was calculated based on the residual amount of granisetron at the time of patch removal. Specifically, the released dose was calculated as the administered dose (initial patch content) minus the residual granisetron amount in the patch after removal. The *in vitro* flux is then calculated as the released dose divided by the number of days of patch application. The sponsor provided the results for several studies after dose normalization to a 52 cm² patch (Table 8). For Study 392MD/26/C, the actual assay for the clinical batch used (# 35073) was 32.7 mg and the

mean residual amount after patch removal was determined to be 11.0 mg. Therefore, the patch released on average 21.7 mg of granisetron over 7 days, i.e., mean “*in vitro* flux” was estimated to be 3.10 mg/day (CV: 16.6%).

Table 8. *In Vitro* Flux, Released Amount of Granisetron Per Day, from Granisetron TDS Patch Across 3 Studies (Dose-Normalized)

Study	392MD/8/C	392MD/11/C			392MD/26/C
Manufacturer	Novosis AG	Novosis AG			Aveva DDS
Patch, cm ²	52	15	33	52	52
Days contact	5	6	6	6	7
Dose, mg	34.3	9.9	21.8	34.3	32.7 ¹
N	84	12	12	12	211
Volunteers/Patients	Patients	Volunteers			Volunteers
Male/Female	27/57	12/0	12/0	12/0	53/158
Delivered dose, mg	16.3	6.4	12.6	22.1	21.7
Mean <i>In Vitro</i> Flux, mg/day (CV%)	3.27 (25.6%) M: 3.36/F:3.26	3.68 (21.0%) -----	3.31 (24.5%) -----	3.68 (13.8%) -----	3.10 (16.6%) M:3.19/F:3.06

¹ Based on the actual assay value for the clinical batch (No.35073).

Reviewer’s comment:

Using the term “*in vitro* flux” can be misleading as it implies that the value was obtained from an *in vitro* study and that the drug release rate from the patch is relatively constant over the intended time period of use (whereas after patch application, it actually varies with a time lapse). We, therefore, consider it as the average daily delivery rate. One should bear in mind that this number is for labeling purpose only and that it does not represent the actual drug delivery rate.

It appears that the drug, after permeating through the skin, can be stored in the subcutaneous adipose tissue first and subsequently released to systemic circulation.

Q5. What was the Primary Efficacy Endpoint in the Pivotal Phase 3 Study 392MD/15/C?

The primary efficacy endpoint used in the pivotal Phase 3 trial was “complete control”, which is defined as no vomiting or retching, no more than mild nausea, and no rescue medication from the first administration until 24 hours after the start of the last day’s administration of the multiday chemotherapy. The response rate for prevention of acute CINV was comparable between the patch and oral granisetron (60.2% vs. 64.8%) according to Dr. Karyn Berry, Medical Officer of HFD-180.

2.3 Intrinsic Factors: Data not available

2.4 Extrinsic Factors: Data not available

2.5 General Biopharmaceutics:

The formulation of GTDS patch is given in Table 9. During the clinical testing of GTDS, the manufacturer of the patch changed from _____ to Aveva DDS Inc. Granisetron TDS patch manufactured by _____ was used in 2 Phase 1 PK studies, 392MD/4/C and 392MD/11/C and in a Phase 2 clinical trial, 392MD/8/C. However, as reported by the sponsor, the same granisetron TDS formulation was taken forward to scale up studies at Aveva DDS Inc. with no changes. The Aveva produced patch was used in the Phase 1 Sensitization and Irritation study (392MD/26/C) and the Phase 3 clinical study (392MD/15/C).

b(4)

Table 9. Composition of Granisetron TDS used in Clinical Studies

Ingredient	Function	% Composition of laminate	Quantity/patch
Granisetron ¹	Active ingredient		34.3 mg
	adhesive		
	Backing material ⁴		52 cm ²
	Release liner ²		1 piece

b(4)

¹ as granisetron base
² removed during the process and not part of the finished product
³ removed prior to patch application
⁴ the backing material is preprinted with an identifier using _____

b(4)

2.6 Analytical Section

The assay method involved liquid-liquid-extraction and chromatographic separation on _____ The standard curve was prepared as follows: 0.10, 0.20, 0.40, 1.0, 2.0, 4.0, 8.0, and 10.0 ng/mL (n=8). The QC samples were prepared at 0.10, 0.30, 1.50, 7.5 ng/mL (n=4).

Q9. Is the assay methods adequately validated?

The assay performance is found to be acceptable (Tables 10-11)

Table 10. Summary of Inter-Assay Performance

Calibrated Range	_____
Defined LOQ	_____
Linearity	_____
Accuracy	_____
Precision	_____

b(4)

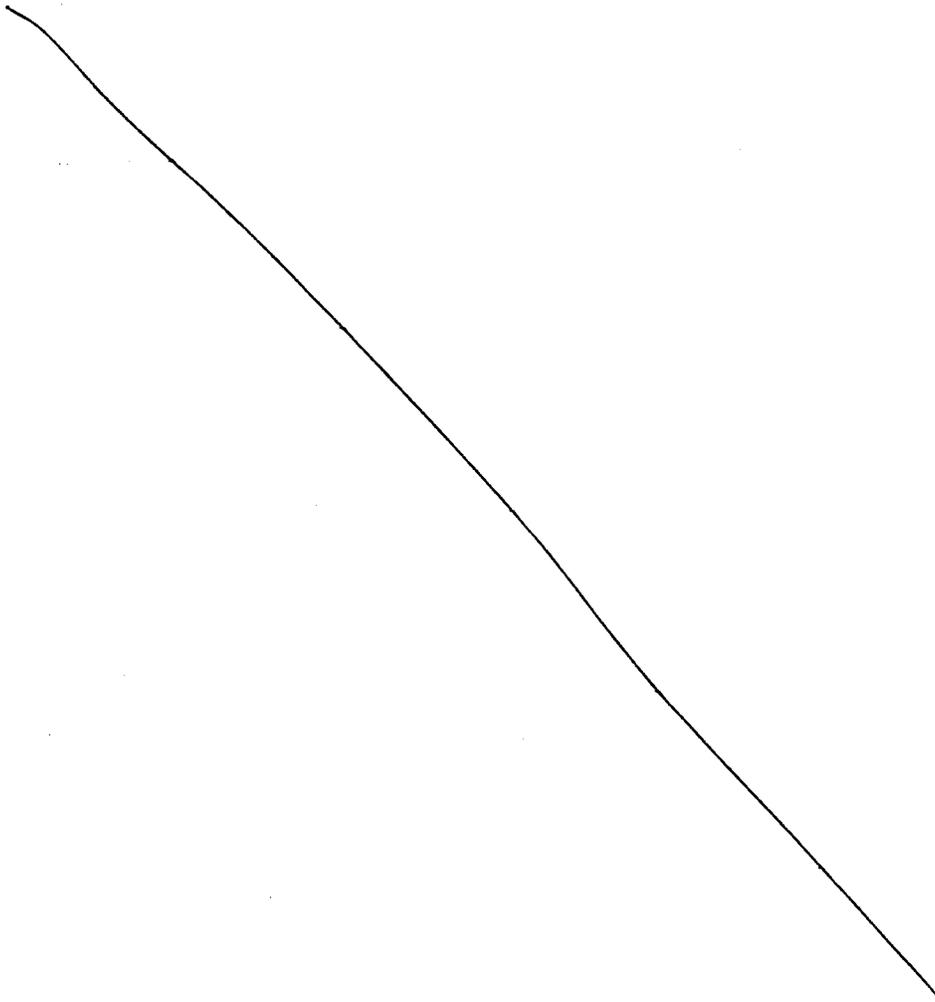
Table 11. Summary of QC Sample for Intra-assay Performance

Conc. [ng/mL]	0.300	1.50	7.50
n	8	8	8
mean	0.310	1.58	7.61
sd	0.0105	0.0332	0.220
cv [%]	<hr/>		
bias [%]	<hr/>		

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3. Detailed Labeling Recommendations

Agency proposed labeling revisions are: addition (blue and underlined) and deletion (~~red and double strikethrough~~) as shown below:



b(4)

b(4)

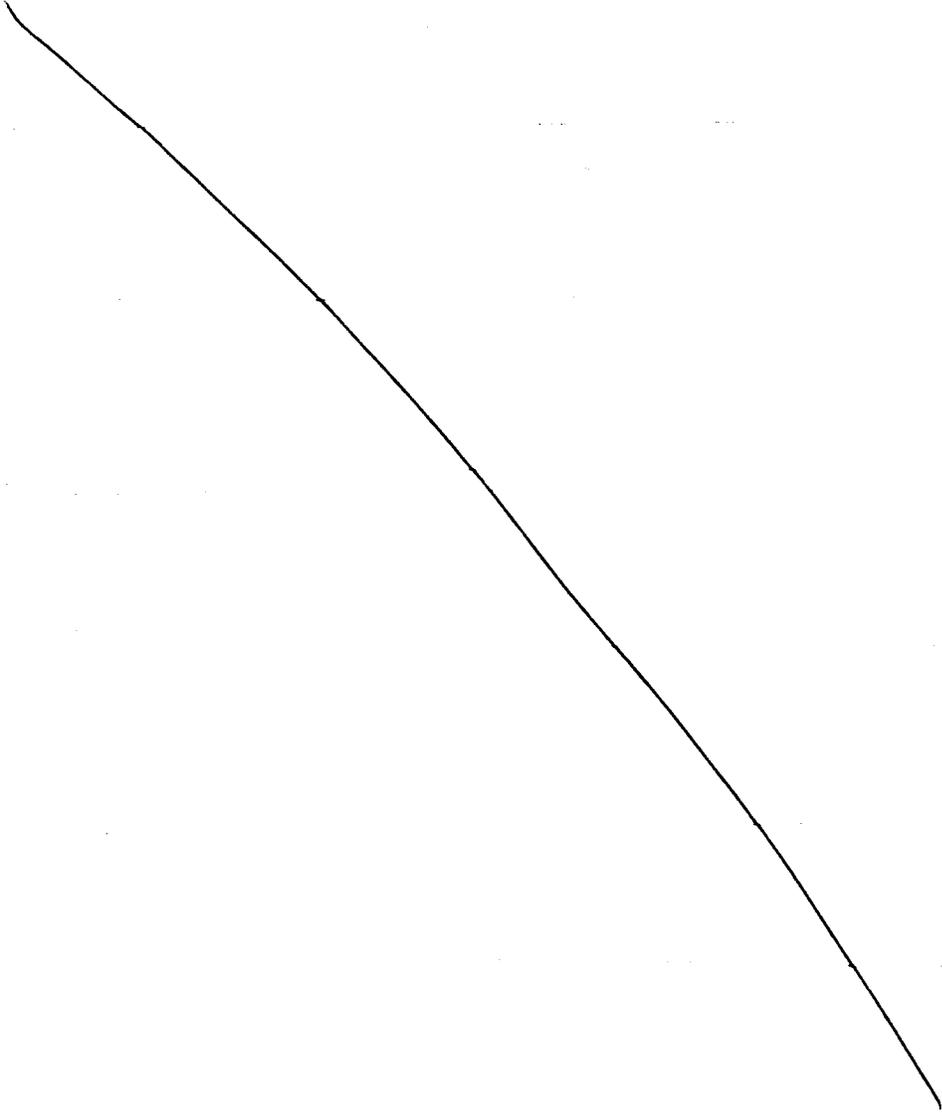
Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)



b(4)

b(4)

b(4)

4. Appendices

- 4.1 Proposed Package Insert
- 4.2 Individual Study Review
- 4.3 Cover Sheet and OCPB Filing/Review Form

**NDA 22-198 for Sancuso Granisetron Transdermal
System (GTDS) Patch**

Appendix 4.1

Sponsor's Proposed Labeling

18 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

**NDA 22-198 for Sancuso Granisetron
Transdermal System (GTDS) Patch**

Appendix 4.2

Individual Study Reports

STUDY SYNOPSIS

Study number 392MD/11/C

Title

Four-way, crossover, open-label, comparative pharmacokinetics study of single application of 3 different dosages of one TDS granisetron formulation applied for 6 days with once daily dosing of 2 mg granisetron tablet (Kevatril®) for 5 days to healthy male subjects

Investigator, study site: _____

Study duration and dates 28 June 2005 to 19 August 2005

Phase I

Objectives

Primary objective: to compare the bioavailability of granisetron after a single 6-day application to the upper outer arm of 3 dosages of one granisetron TDS formulation to that of 2 mg once daily dose of granisetron tablet (Kevatril®) for 5 days.

Secondary objectives: to assess the dose proportionality of granisetron pharmacokinetics after a single TDS application for 6 days as well as local tolerance, safety, tolerability and the adhesion of granisetron TDS.

Study design

Open, single center, 4-treatment-4-period crossover study with four randomized administrations of granisetron as TDS or tablet.

Number of subjects planned

A total of 12 subjects were planned to be included in this study.

Inclusion criteria

Subjects meeting all of the following criteria were considered for enrollment into the study:

- Healthy male subjects aged between 18 and 45 years with body mass index of between 19 and 28 kg/m²
 - Non-smoker since at least 3 months.
 - Sun reactive skin type I, II, III or IV.
 - Normal findings in the medical history, physical examination, normal 12-lead ECG, blood pressure and pulse rate unless the investigator considered the abnormality not to be clinically relevant.
 - Laboratory values within the normal range or judged not relevant by the investigator. For AST and ALT, the values were to be strictly within the normal range.
 - Were to be willing and able to participate in the whole study and must provide written informed consent prior to any assessments being taken.
-

Treatments

Subjects received the 4 following treatments according to a randomized design:

- A: Once daily dose of 2 mg granisetron tablet (Kevatril®) for 5 days.
 - B: TDS of 52-cm² granisetron 6% (34.3 mg) applied for 6 days on the upper outer arm.
 - C: TDS of 33-cm² granisetron 6% (21.8 mg) applied for 6 days on the upper outer arm.
 - D: TDS of 15-cm² granisetron 6% (9.9 mg) applied for 6 days on the upper outer arm.
-

b(4)

Study number 392MD/11/C

Pharmacokinetic data

Serial blood samples were taken before and up to 240 hours after TDS application (e.g up to 96h after TDS removal) and up to 72 hours after the last oral dose. Plasma concentrations of granisetron were assessed using an HPLC-fluorescence method with a limit of quantification of 0.1 ng/mL. The following pharmacokinetic parameters were calculated: C_{max}, t_{max}, t_{1/2,λz}, AUC(0-z), AUC(0-∞), in vivo flux (for TDS only) and C_{avg} calculated as AUC(0-24h)_{ss}/24 for oral dosing and as AUC(0-144h)/144 for TDS application. The apparent elimination half-lives (t_{1/2}, λ_z) were calculated by non-compartmental analysis.

Safety data

Local tolerance was assessed by a scoring system, clinical examination and occurrence of adverse events

Statistical procedures

Pharmacokinetics: Descriptive statistics were calculated for plasma concentrations and pharmacokinetic parameters of granisetron.

Oral: Day effect was assessed by means of an analysis of variance with subject and day effects in the model on the following Ln-transformed parameters: C_{max}, C_{avg}, t_{1/2,λz} and AUC(0-∞). As t_{max} is a discrete variable, day effect was tested using a Kruskal-Wallis non-parametric test.

Time for plasma concentrations of granisetron to reach steady state was assessed on Ln-transformed trough plasma concentrations (C_{24h}) observed from days 1 to 5 using an analysis of variance with subject and day as main effects in the model followed by a Tukey's test.

TDS: Proportionality between the dose administered (size of the patch) and the pharmacokinetic parameters was assessed by means of an analysis of variance with subject, dose and period interaction as main effects in the model on the following Ln-transformed parameters: C_{avg}/dose, AUC(0-∞)/dose, in vivo flux/dose and t_{1/2,λz}.

Local tolerance: The main analysis was based on descriptive statistics on irritation score and other clinical observations

Interim analysis

There was no interim analysis.

Results - Study subjects and conduct

A total of 12 healthy subjects aged between 25 and 42 years (mean: 37.1 years) and weighing between 64.1 and 92.2 kg (mean: 76.8 kg) were included in this study. All of them completed the study and were included in the local tolerance and safety analyses.

Results - Pharmacokinetics

Treatment A: Granisetron pharmacokinetic parameters [mean (CV%)] after once daily 2 mg oral dose for 5 days are given in the table below:

		Day 1 (N=12)	Day 5 (N=12)
C _{max}	(ng/mL)	5.25 (42)	5.5 (58)
C _{avg}	(ng/mL)	2.14 (80)	2.60 (110)
t _{max}	(h) a	1.5 [1-4]	2 [1-4]
t _{1/2,λz}	(h)	6.4 (74)	7.9 (74) b

a: median [range] b: n=11

Granisetron steady state was reached after the second dosing day. No accumulation of granisetron was observed either on C_{max} and C_{avg}. Between-subject variability was high (CV of 42 - 68% for C_{max} and of 80-120% for AUC).

Study number 392MD/11/C

Treatments B, C and D: Granisetron pharmacokinetic parameters [mean (CV%)] after granisetron TDS application for 6 days are given in the table below:

		52 cm ² (Treatment B; N=12)	33 cm ² (Treatment C; n=12)	15 cm ² (Treatment D; N=12)
Cavg	(ng/mL)	2.23 (89)	1.24 (110)	0.68 (83)
t _{1/2}	(h)	35.9 (35)	30.9 (21) d	30.9 (32) c
In vivo flux	(mg/24h)	3.30 (93)	1.90 (110)	1.02 (88)

c: n=10 d: n=8

Mean Cavg of granisetron increased in proportion to the patch size increased. The between-subject variability of the granisetron pharmacokinetics after patch application was high (CV of 83-110% for Cavg).

Results – Safety

Skin tolerability was acceptable for the three dosages of granisetron TDS formulation.

Patch adhesiveness was good. Nearly all applied patches were properly adhered and only 2 of 36 patches were completely unstuck.

Safety measurements (laboratory results, vital signs, physical findings and ECG's) did not show any clinically relevant changes during the study.

Regarding the general safety, there were no major differences between the four treatments. No serious adverse event was reported during this study. A total of 27 TEAEs were reported during the study in 10 subjects. Among them, 20 reported in 9 subjects (75%) were considered by the investigator to be drug related and mainly concerned the nervous system (dizziness reported in 8.3% after treatment A and headache reported in 8.3%, 25% and 41.7 % of the subjects after treatments B, C and D) and the gastrointestinal system (constipation reported in 8.3% and 16.7% of the subjects after treatment B and D). The adverse events were of mild or moderate intensity except one headache reported after application of treatment D as severe. Whatever the event, the study medication was unchanged and events related to study medication resolved spontaneously.

Conclusions

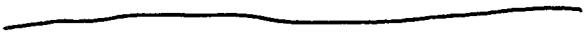
A 52 cm² granisetron TDS resulted in similar Cavg concentration to once daily oral dosing of 2 mg granisetron. The granisetron in vivo delivery rate was of 3.30 mg/day for the 52 cm² patch

Granisetron pharmacokinetics were proportional to the granisetron TDS size. Within-subject variability of granisetron pharmacokinetics was moderate with values of 31 to 42% for Cavg and AUC whereas between-subject variability was high (CV on Cavg and AUC with values ranging from 70 to 110%) but comparable to the between-subject variability observed after oral dosing (CV ranging from 42 to 68% for Cmax and from 80 to 120% for AUC).

Overall, the three dosages of the granisetron TDS formulation were well tolerated both locally and systemically.

Reviewer's Comment:

The study results were reviewed and found acceptable.

Title:	A double-blind, placebo controlled study to assess the cumulative skin irritation and sensitization potential of the granisetron transdermal delivery system (GTDS)
Protocol Identification:	 Strakan Pharmaceuticals Ltd code: 392MD/26/C
Clinical Phase:	Phase I
Subject Population/Indication:	Healthy subjects
Design:	Single centre, double-blind placebo controlled study.
Sponsor:	Strakan Pharmaceuticals Ltd
Investigational Product:	Granisetron transdermal delivery system (GTDS) 6% w/w
Principal Investigator:	Dr Catherine Queille-Roussel, M.D.
Treatment duration:	Twenty-one (21) days (Induction Phase) Two days (Challenge Phase)
Dose:	34.3 mg of granisetron or placebo by patch
Study Initiation Date:	First subject in: 26-Aug-2006
Study Completion/ Termination Date:	Last subject out: 02-Nov-2006
Study Report Date:	Final Version: 07-Jun-2007

b(4)

2. SYNOPSIS

Name of Sponsor/Company: STRAKAN PHARMACEUTICALS LTD	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Investigational Product: Granisetron transdermal delivery system (GTDS)	Volume: Page:	
Name of Active Substance: Granisetron		
Title: A double-blind, placebo controlled study to assess the cumulative skin irritation and sensitization potential of the granisetron transdermal delivery system (GTDS)		
Investigator: _____		
Study Center:	_____	
Publication (reference): Not applicable.		
Study Design: Single centre, double-blind placebo controlled study		
Studied period (years): 26-Aug-2006 to 02-Nov-2006	Phase of development: Phase I	
Study Objectives: The aim of the study was to assess the skin irritation, and sensitization potential of the GTDS. Primary Objectives: -To assess the incidence and prevalence of irritation at the site of application after repeated applications of the study drug materials (Induction Phase). -To assess the incidence of sensitization at an alternative skin site after another application of the study drug materials (Challenge Phase). Secondary Objectives: -To assess the delivery of granisetron from the patch by determining the plasma granisetron levels in a subset of subjects.		
Methodology: The study was a single centre, double-blind placebo controlled study. The study consisted of a 28-day screening period, a 3-week Induction Phase followed by a Rest Phase of 2 weeks and a subsequent Challenge Phase of 6 days. If required, an additional 1-week re-Challenge Phase was to be completed. A 7-10-day follow up phase was completed by all subjects. During the Induction Phase, a total of 3 applications of the 2 test products (active and placebo patches) were performed on the upper outer arms. The patches remained in place for 1 week. The skin reactions were assessed prior to patch application on Day 1 and at 30 minutes after each patch removal on Days 8, 15 and 22. During the Challenge Phase, the 2 test products were applied for 48 hours (hrs) on the back and skin sensitization was scored 30 minutes, 24, 48 and 72 hrs after patch removal. In case of an eventual re-challenge, this procedure was to be repeated within 14 days. Additionally, patch adhesion and subjective assessments was evaluated 3 times each week during the Induction Phase and after 48 hrs during the Challenge Phase.		

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Name of Sponsor/Company: STRAKAN PHARMACEUTICALS LTD	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of Investigational Product: Granisetron transdermal delivery system (GTDS)	Volume: Page:	
Name of Active Substance: Granisetron		
Number of subjects (planned and analyzed): 210 subjects to achieve 200 subjects completing the study. Subset of 24 subjects for PK blood samples to determine plasma granisetron levels. In total: 210 subjects planned, 212 enrolled. 201 analyzed for irritation, 200 for sensitization.		
Diagnosis and main criteria for inclusion: Healthy male or female subjects between 18 and 65 years.		
Route of administration and dosage, batch number: Topical administration. Granisetron 34.3 mg transdermal patch for 3, 7-day periods. Batch number: 35073 – Expiry date: 10/2007		
Duration of treatment: Induction Phase: 1 application (placebo and active) per week for 3 weeks (i.e. a total of 3 active and 3 placebo patches over 3 weeks). Challenge Phase: 1 application (placebo and active) for 48 hrs.		
Reference therapy, route of administration and dosage, batch number: Topical administration. Placebo transdermal patch for 3, 7-day periods. Batch number: 35048– Expiry date: 10/2007		
Criteria for Evaluation: Efficacy: Not applicable		

Name of Sponsor/Company: STRAKAN PHARMACEUTICALS LTD	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of Investigational Product: Granisetron transdermal delivery system (GTDS)	Volume: Page:	
Name of Active Substance: Granisetron		
<p>Safety:</p> <p>Safety assessment consisted of:</p> <ul style="list-style-type: none"> • Local tolerance assessment <p>The following criteria were evaluated:</p> <p>- Induction Phase: The dermal response was scored at Day 1 and 30 minutes after removal of each patch. The following grading scale was used:</p> <p>0: No reaction 1: Slight erythema (faint pink to definite pink) 2: Moderate erythema (definite redness) 3: Severe erythema (very intense redness) or erythema with edema 4: Erythema with vesicles or erosion or bullae</p> <p>- Challenge Phase: The dermal response was scored 30 minutes, 24, 48 and 72 hrs after removal of the challenge patch using the following scale:</p> <p>0 No reaction 1 Erythema without edema 2 Erythema with edema or small papules 3 Erythema with individual vesicles 4 Erythema and swelling with blisters</p> <p>- Subjective comments reported by the subjects such as pruritus, stinging, burning sensation were also recorded during the Induction and Challenge Phase as follows:</p> <p>1 = Weak 2 = Moderate 3 = Severe</p> <p>- Other local reactions observed during the Challenge Phase were scored as follows:</p> <p>C = Chaps, cracking or fissures. D = Desquamation (shedding of the outer layers of the skin). Pu = Pustules (inflammatory small elevations containing yellow-white exudates). W = Weeping/oozing [may be a sign of vesiculation or blister (epidermal damage) manifested by crusting]. S = Extension of the reaction beyond patch-test site (on skin area where no test product was applied).</p> <p>- Sensitization reaction: At the last reading of the Challenge Phase, the Investigator gave an opinion concerning a possible sensitization reaction, using the scale below :</p> <p>0 = Negative 1 = Equivocal 2 = Positive</p>		

Name of Sponsor/Company: STRAKAN PHARMACEUTICALS LTD	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of Investigational Product: Granisetron transdermal delivery system (GTDS)	Volume: Page:	
Name of Active Substance: Granisetron		
<ul style="list-style-type: none"> • Patch adhesion <p>Adhesion of the patch delivery systems was evaluated at each visit. Patch adherence was the estimate of the percentage of the patch surface in contact with the skin. It was graded from 0-4 on a 5-point scale as follows:</p> <p>0 = patch adhered >90% (completely on) 1 = patch adhered 75-90% (edges lifting off) 2 = patch adhered 50-74% (half-off) 3 = patch adhered <50% (just hanging on) 4 = patch not present on skin</p> <ul style="list-style-type: none"> • Pharmacokinetics (Subset of 24 subjects) <p>In a subset of consenting subjects (12 males and 12 females), 10 ml blood samples for determination of granisetron concentration were drawn at pre-dose and at 8, 24, 48, 72, 96, 120, 144, and at 168 hrs after the first patch application. The last sample was taken after the first patch had been removed and before the second patch application.</p> <ul style="list-style-type: none"> • Adverse event (AE) recording at each visit 		
<p>Statistical Analyses Planned:</p> <p>The individual observations were provided, as well as a tabulation of the percentage of subjects with each grade of skin reaction and degree of patch adherence on each observation day.</p> <p>The mean cumulative irritation score and the total cumulative irritation score for all study subjects were calculated for each test product and a statistical analysis of the comparative results were performed according to the FDA guidelines¹.</p> <p>A narrative description of each reaction in the Challenge Phase was provided, together with the opinion of the Investigator, as to whether such reactions were felt to be indicative of contact sensitization.</p>		
<p>Summary – Conclusion</p> <p>Efficacy Results: Efficacy was not assessed in this study.</p>		

Name of Sponsor/Company: STRAKAN PHARMACEUTICALS LTD	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use only)</i>
Name of Investigational Product: Granisetron transdermal delivery system (GTDS)		
Name of Active Substance: Granisetron		

Safety Results:

Irritant potential (Induction Phase): number (N) of subjects = 201

Incidence and prevalence of skin irritation were calculated. Incidences of positive irritant reaction (percentage of subjects who experienced a skin reaction scored >1) are presented below for the two test products.

N (%)	Day 8	Day 15	Day 22
GTDS	27 (13.43)	12 (5.97)	13 (6.47)
Placebo	45 (22.39)	24 (11.94)	32 (15.92)

Mean cumulative irritation score and total cumulative scores were also calculated and the granisetron transdermal delivery system (GTDS) was compared to the placebo. Results are presented below.

Parameters		GTDS	Placebo	Non-inferiority Test <i>P</i>
<i>Mean cumulative irritation (MCI) score</i>	<i>Mean SD</i>	0.64 0.54	1.00 0.67	<i>P (t) < 0.0001</i>

Parameters		GTDS	Placebo	Non-inferiority Test <i>P</i>
<i>Total cumulative irritation (TCI) score</i>	<i>Mean SD</i>	1.92 1.63	3.00 2.00	<i>P (t) < 0.0001</i>

The two patches (active and placebo) were considered as slightly irritant.

Sensitization potential (Challenge Phase): n= 200 subjects

One positive sensitization reaction to the active patch was observed during the Challenge Phase.

Positive diagnosis of allergic contact reaction to the granisetron patch was based on coexistence of the following symptoms:

- skin reaction scored 3 (erythema with individual vesicles)
- delayed marked pruritus (no score, reported after the Day 3 assessment)
- extension of the reaction beyond the patch-test site (on skin area where no test product was applied)
- kinetics of the skin reaction.

No sensitization reaction was observed with the placebo.

Name of Sponsor/Company: STRAKAN PHARMACEUTICALS LTD	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of Investigational Product: Granisetron transdermal delivery system (GTDS)	Volume: Page:	
Name of Active Substance: Granisetron		
<p>Adverse Events:</p> <p>A total of 580 AEs were reported. Seventy-seven percent were regarded as related. During the clinically relevant first week, 53.3% of subjects reported constipation, 25.5% reported headache, and 10.4% reported abdominal pain. One subject withdrew due to constipation in the first week.</p> <p>No clinically significant changes in laboratory values were detected.</p> <p>One serious AE occurred, cerebral vascular accident, and was considered as not related to the study medication.</p> <p>No other unexpected safety issues have arisen.</p>		
<p>Conclusion:</p> <p>This study was conducted as a randomized double-blind placebo controlled intra-individual comparison in healthy subjects. Two hundred and twelve healthy subjects aged 19 to 63 years were randomized. Two hundred and one subjects were eligible for assessing the skin irritant potential. Two hundred were eligible for assessing the sensitization potential.</p> <p>Determination of incidence and prevalence of skin irritation reactions showed that the active granisetron patch was no more irritant than its matching placebo patch. The two patches proved to be slightly irritant, with prevalence at Day 8 of 13% (active) and 22% (placebo).</p> <p>One positive contact allergic reaction was detected out of the 200 subjects eligible for the sensitization potential analyses (0.5%).</p> <p>Application of a patch was discontinued in 5 subjects due to serious irritant reactions at the original patch site. The patch was applied at a different site in 4 out of the 5 subjects. Other skin reactions were modification of skin pigmentation observed during the follow-up on the patch test sites in 36 subjects regardless of the patch, active or placebo. This was thought by the Investigator to be due to adhesive stripping of tanned skin.</p> <p>A total of 580 AEs were reported during the study. However, a great majority of these AEs were expected according to the product characteristics and are commonly reported with 5-HT₂ receptor antagonists (headache, digestive symptoms). It is likely that the threshold for AE reporting in healthy subjects is much lower than in ill patients receiving chemotherapy. Only 5% of events thought to be related to the study products were severe. One serious AE was reported (cerebellous vascular accident) but was not attributed to the study products. No other unexpected safety issues have arisen.</p> <p>Patch adhesivity was assessed 3 times a week during the Induction Phase and at Day 3 (patch removal) during the Challenge Phase to validate the assessments. Reinforcement of the patches with adhesive dressings was authorized to ensure appropriate compliance where appropriate. In the Induction Phase, 94.5% of subjects had $\geq 75\%$ patch adherence by Day 8 with the GTDS in the Induction Phase and 89% of subjects had $\geq 75\%$ patch adherence with the GTDS in the Challenge Phase. This confirms that the compliance was good and validates the study results.</p> <p>From the study data, it can be concluded that both the active granisetron patch and its matching placebo are slightly irritant when applied on healthy skin with a lower number of subjects reporting irritation with the active patch than the placebo patch. A low sensitization potential (0.5%) was detected for the active granisetron patch. No sensitization potential was detected for the placebo.</p>		
<p>Date of Report: Final Report : 07-Jun-2007</p>		

Reviewer's Comment:

The study results were reviewed and found acceptable. Additional analyses on gender difference were made. Please see review text for details.

**NDA 22-198 for Sancuso Granisetron
Transdermal System (GTDS) Patch**

Appendix 4.3

Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-198	Brand Name	Sancuso
OCPB Division (I, II, III)	DCP III	Generic Name	Granisetron
Medical Division	GI and Dermatology	Drug Class	Anti-emetics
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	Prevention of CINV
OCPB Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	Skin Patch (52 cm ²)
		Dosing Regimen	One patch for up to 7 days
Date of Submission	06/29/07	Route of Administration	Transdermal
Estimated Due Date of OCPB Review	05/10/08	Sponsor	Strakan Pharmaceuticals
Medical Division Due Date	05/15/08	Priority Classification	Standard
PDUFA Due Date	Extended to 06/10/08		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	1	1	
I. Clinical Pharmacology	x			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	x			
Healthy Volunteers-				
single dose:		2	2	
multiple dose:		1	1	
Patients-				
single dose:		2	2	Clinical (one pivotal Phase 3 and one supportive Phase 2)
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	x			
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		6	6	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Did GTDS patch application provide comparable PK and as well as clinical benefit with Kytril oral dosing?			
Other comments or information not included above				
Primary reviewer Signature and Date	Tien-Mien Chen, Ph.D. 08/23/07			
Secondary reviewer Signature and Date	Sue-Chih Lee, Ph.D. 08/23/07			

APPEARS THIS WAY ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tien-Mien Chen
7/3/2008 07:53:54 PM
BIOPHARMACEUTICS

Sue Chih Lee
7/3/2008 07:56:39 PM
BIOPHARMACEUTICS