

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-198**

**STATISTICAL REVIEW(S)**

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**NDA/Serial Number:** 22198  
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**Drug Name:** Sancuso® (Granisetron Transdermal System)  
**Indication:** Prevention of nausea and vomiting associated with \_\_\_\_\_  
\_\_\_\_\_ courses of moderate or highly emetogenic cancer  
chemotherapy  
**Applicant:** Strakan International Limited  
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## 1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

### 1.1 Conclusions and Recommendations

From a statistical perspective, the single pivotal Study 392 MD/15/C does not provide substantial evidence to support the conclusion that the GTDS patch is non-inferior to oral granisetron in prevention of nausea and vomiting associated with initial and repeat courses of moderate or highly emetogenic cancer chemotherapy. This conclusion does not imply the GTDS patch should be judged ineffective in the pivotal study.

However, the lower bound for the two-sided 95% confidence interval on the proportion of complete control in the acute phase for GTDS patch is not less than 0.50, calculated using pivotal Study 392 MD/15/C. Using this result as a reference, if the medical division deems that the complete control rate in the acute phase would be higher than that of placebo, then, the GTDS patch can be considered effective.

### 1.2 Brief Overview of Clinical Studies

The applicant submitted two studies to support the use of Granisetron TDS (GTDS) in prevention of nausea and vomiting associated with initial and repeat courses of moderate or highly emetogenic cancer chemotherapy. Study 392 MD/8/C was a phase 2 supportive study and Study 392 MD/15/C was a phase 3 pivotal study. Both studies compared GTDS to oral granisetron.

The objective of Study 392MD/8/C was to assess the effect of Granisetron TDS patch based upon the primary endpoint of the total control for chemotherapy induced nausea and vomiting (CINV) for the period 24 - 120 hours (delayed phase) post single-day moderate emetogenic chemotherapy, while that of Study 392MD/15/C was to evaluate the effect of Granisetron TDS patch based upon the primary endpoint of the complete control for CINV from the first administration until 24 hours (acute phase) post moderate emetogenic (ME) or highly emetogenic (HE) chemotherapy following multi-day chemotherapy. For the supportive study, the endpoint used was total control, defined as no nausea, no vomiting, no use of rescue medication, and no withdrawal from the study; for the pivotal study, the endpoint was complete control, defined as no vomiting, no more than mild nausea, and no rescue medication. The differences in these studies are further addressed in Section 2.0.

### 1.3 Statistical Issues and Findings

#### 1.3.1 Phase 2 Study 392 MD/8/C

The applicant's two studies (392 MD/15/C & 392 MD/8/C) differed in objective, inclusion/exclusion criteria, primary assessment period, duration of patch application, duration of chemotherapy application, primary endpoint, and the efficacy analysis. As a result, the supportive Study 392MD/8/C does not provide direct evidence of replication in support of the

single pivotal study.

In addition, as for the primary endpoint (total control in the delayed phase) analysis, the applicant's assertion of comparability between the two treatments is based upon a non-significant result of a superiority analysis for testing the null hypothesis of no treatment effect difference is not scientifically valid. Finally, the lower bound of the two-sided 95% confidence interval for complete control in the acute phase for GTDS minus oral granisetron is -26%, much less than the -15% margin set up for the primary endpoint (CC for the acute phase) for the pivotal study. This result suggests that the efficacy of the study drug, with respect to CC, may be inferior to that of oral granisetron by more than 15%.

Consequently, it appears that no efficacy evidence is provided by Study 392MD/8/C to support the pivotal Study 392MD/15/C for GTDS patch in use of the proposed indication. The efficacy assessment of the study drug GTDS should mainly rely on the single pivotal Study 392 MD/15/C.

### 1.3.2 Phase 3 Study 392 MD/15/C

The following analyses and comments on the efficacy assessments are for the non-inferiority of GTDS patch versus oral granisetron based upon the primary endpoint - complete control for the first 24 hour from the first administration until 24 hours after the start of the last day's administration of the ME or HE chemotherapy regimen.

- The applicant's logistic regression analysis and this reviewer's simple proportion (un-adjusted) analysis show that the lower bounds of the two-sided 95% confidence intervals for the proportion of complete control are close to the non-inferiority margin of -15% (-13.0% and -12.40% respectively for logistic regression and simple proportion analyses). In addition, since the complete control rate of GTDS patch is 5.0% less than that of oral granisetron, this result indicates that the non-inferiority conclusion is not robust.
- Following the efficacy assessment criteria for the superiority analysis of a single clinical trial, a much higher level of confidence is recommended to be applied, for example, 99.75%. The lower bound of the two-sided 99.75% is -17.0%, less than the non-inferior margin of -15%; this also suggests, that the evidence for non-inferiority of the GTDS patch to oral granisetron as assessed by complete control provided by this single study is not substantial.
- The applicant's analysis on the complete response (no vomiting and no rescue therapy) indicates that the lower bounds of the two-sided 95% confidence intervals for the complete response are -14.4% and -15.3% respectively, for PPS and FAS populations. Because of the two lower bounds either very close (-14.4% from PPS) to or smaller (-15.3% from FAS) than the negative non-inferiority margin (-15%), the efficacy of GTDS is very likely inferior to that of oral granisetron by more than 15 percent even assessed at the regular two-sided 95% confidence interval normally used for two pivotal studies. Since the 15% non-inferiority margin selected by the applicant is mainly based upon



\_\_\_\_\_ moderate or highly emetogenic cancer chemotherapy. The applicant emphasized that Study 392 MD/8/C was a phase 2 supportive study and Study 392 MD/15/C was a phase 3 pivotal study. However, it is noted that the two studies differed in their objective, inclusion/exclusion criteria, primary assessment period, duration of patch application, duration of chemotherapy application, primary endpoint, and the efficacy analysis method. The details of the differences between the two studies are briefly stated below.

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The objective of Study 392MD/8/C was to assess the effect of Granisetron TDS patch based upon the primary endpoint of the total control for chemotherapy induced nausea and vomiting (CINV) for the period 24 - 120 hours (delayed phase) post single-day moderate emetogenic chemotherapy, while that of Study 392MD/15/C was to evaluate the effect of Granisetron TDS patch based upon the primary endpoint of the complete control for CINV from the first administration until 24 hours (acute phase) post moderate emetogenic (ME) or highly emetogenic (HE) chemotherapy following multi-day chemotherapy. For Study 392MD/8/C, the endpoint used was total control, defined as no nausea, no vomiting, no use of rescue medication, and no withdrawal from the study while for the pivotal study(392MD/15/C), the endpoint was complete control, defined as no vomiting, no more than mild nausea, and no rescue medication.

There were also differences between the two studies in inclusion and exclusion criteria; for example chemotherapy naïve (392MD/8/C) vs. no restriction on chemotherapy naïve (392MD/15/C) and concomitant use of dexamethasone.

As for the duration of patch application, for study 392MD/8/C, patients applied the patch 24 hours before receiving their chemotherapy treatment and wore the patch for a total of 5 days while for Study 392MD/15/C, patients applied the patch 24 to 48 hours before chemotherapy and wore the patch for a total of 7 days.

Finally, for the efficacy analysis, Study 392MD/8/C was planned to apply a superiority analysis to test the null hypothesis that the granisetron TDS patch was not different from the single oral dose of granisetron.

\_\_\_\_\_ For Study 392MD/15/C, the applicant applied a non-inferiority analysis to test the null hypothesis that the GTDS was not inferior to oral granisetron. However, there were no historical studies conducted under similar conditions to that of Study 392MD/15/C to assess the efficacy of active control versus placebo to support the selected non-inferiority margin of 15%.

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Table 2.1.1 summarizes the two efficacy studies (392 MD/8/C and 392 MD/15/C) for Granisetron TDS patch.

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drug similar in efficacy to a standard agent. Most of these are actually non-inferiority trials, attempting to show that the new drug is not less effective (inferior) than the control by more than a defined amount, generally called margin.

Instead of using a non-significant result \_\_\_\_\_, the applicant should have chosen an adequate delta margin ( $\Delta > 0$ ) following the guidance stated in ICH E10. Then, with the selected margin ( $\Delta$ ), in order to demonstrate clinical equivalence between granisetron TDS (GT) and single oral dose of granisetron (GO), the following two null hypotheses formulated by the proportion of total control (primary endpoint) would \_\_\_\_\_ be rejected:

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$H_{01}: P_{GT} - P_{GO} \leq -\Delta$  or  $H_{02}: P_{GT} - P_{GO} \geq \Delta$ ;

where  $P_{GT}$  and  $P_{GO}$  are the rates of total control for granisetron TDS and single oral dose of granisetron, respectively.

Finally, at 0.025 significant level, a 95% two-sided confidence interval on the difference of  $P_{GT}$  and  $P_{GO}$  can be constructed to test the null hypothesis  $H_0: U_{i=1, 2} H_{0i}$ . If the 95% two-sided confidence interval is included in the interval  $(-\Delta, \Delta)$ , \_\_\_\_\_

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As a result, to demonstrate the equivalence of the two drugs granisetron TDS patch and single oral dose of granisetron, \_\_\_\_\_ selected an adequate margin ( $\Delta$ ) and shown that the 95% two-sided confidence interval on the difference of two success rates for granisetron TDS patch and single oral dose of granisetron was included in the interval  $(-\Delta, \Delta)$ . \_\_\_\_\_

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#### Analysis on the complete control

Since the primary endpoint for the pivotal study is the percentage of patients achieving complete control (CC) of CINV from the first administration until 24 hours after the start of the last day's administration of the ME or HE chemotherapy regimen (acute phase), for this supportive study 392MD/8/C, this reviewer also analyzes the CC proportions in the corresponding acute phase for the two drugs (GTDS patch and oral granisetron). Table 2.1.1.1 presents the 95% two-sided confidence intervals for the proportion difference of CC between GTDS patch and oral granisetron during the acute phase (0-24 hours).

**Table 2.1.1.1 (Reviewer's) proportions of complete control during the acute phase**

ENDPOINT	GTDS (G) (n/N)	Comparator <sup>†</sup> (C) % (n/N)	Proportion Dif. G - C	95% two-sided CI for G-C
Complete control of CINV during the first 24 hours	48.0% (42/87)	60.0% (50/84)	-12%	(-26.0%, 3.7%)

<sup>†</sup>: Oral Granisetron

Table 2.1.1.1 indicates that the lower bound of the two-sided 95% confidence interval for the proportion difference (-12%) of CC for GTDS minus oral granisetron is -26%, much less than the negative non-inferiority margin (i.e., -15%) set up for the primary endpoint (CC during the corresponding acute phase) of the pivotal Study 392MD/15/C.

#### Overall comment

First, with the impact of the differences between the two studies (392MD/8/C and 392MD/15/C) noted in the Section 2.1, the supportive Study 392MD/8/C is not considered to provide direct support for the pivotal Study 392MD/15/C in prevention of nausea and vomiting: \_\_\_\_\_ of moderate or highly emetogenic cancer chemotherapy.

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Then, based upon the following two efficacy assessments, it appears that no conclusive efficacy data/evidence is provided by Study 392MD/8/C to support the pivotal Study 392MD/15/C for GTDS in use of the proposed indication:

- 1) The comparability assertion for total control in the delay phase for the two treatments (GTDS patch versus oral granisetron) based upon a non-significant result of a superiority analysis for testing the null hypothesis of no treatment effect difference is not correct and therefore, is not established.
- 2) The lower bound (-26%) of the two-sided 95% confidence interval for the proportion difference of complete control (CC) for GTDS minus oral granisetron is much less than the negative non-inferiority margin of -15% set up for the primary endpoint (CC for the acute phase) of the pivotal Study 392MD/15/C. This result suggests that the efficacy of the study drug GTDS patch is inferior to that of oral grainsetron by more than 15 percent if assessed by the primary endpoint proposed for the pivotal Study 392MD/15/C.

This phase 2 study is not further reviewed. Section 3.0 addresses review of the pivotal study

#### 2.2 Data Sources

To assess the clinical efficacy of GTDS in the prevention of nausea and vomiting associated with initial and repeat courses of moderate or highly emetogenic cancer chemotherapy, this reviewer reviewed the electronic NDA submission dated July 2, 2007 and located at "\\CDSESUB1\NONECTD\N22198\N\_000\2007-06-29". In addition, this reviewer also reviewed the applicant's response documents to the Agency's information request letter dated October 4, 2007 and located at "\\CDSESUB1\NONECTD\N22198\N\_000\2007-11-21".

### 3.0 STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy for Phase 3 Study 392 MD/15/C

##### 3.1.1 Study Design and Endpoints

The primary objective of the study was to demonstrate non-inferiority of the GTDS efficacy as compared to oral granisetron efficacy with regard to complete control (CC) of CINV (CC defined as no vomiting and/or retching, no more than mild nausea, and no rescue medication) from the first administration until 24 hours (acute phase) after the last administration of the moderately (ME) or highly (HE) emetogenic multi-day chemotherapy according to Hesketh classification.

The secondary objectives were to compare the Granisetron TDS to oral granisetron using other efficacy parameters:

- CC of CINV during successive 24 hours (h) intervals from the first administration until 24 h after the last administration of the cytotoxic agents(s) with ME or HE potential.
- Time to first emetic episode and number of emetic episodes from the first administration until 24 h after the last administration of the ME or HE multi-day chemotherapy.
- Complete response (CR; defined as no vomiting or retching and no rescue medication) of CINV from the first administration until 24 hours after the last administration of the ME or HE chemotherapy and during successive 24 hour intervals from the first administration of ME or HE chemotherapy until 24 hours after the last administration of the ME or HE multi-day chemotherapy.

This was a randomized, active control, double-blind, double-dummy, parallel-group, multi-national Phase III study to assess the efficacy, tolerability, and safety of the granisetron transdermal delivery system (GTDS) in chemotherapy-induced nausea and vomiting (CINV) associated with the administration of moderately or highly emetogenic multi-day chemotherapy.

Patients were randomized in 60 of centers: 9 centers in Bulgaria, 2 centers in the Czech Republic, 10 centers in India, 5 centers in Mexico, 3 centers in Poland, 8 centers in Romania, 12 centers in Russia, 9 centers in the USA and 2 centers in Serbia and Montenegro. The first patient was enrolled on 24 January 2006 while the last patient was completed on 11 October 2006. It was planned to recruit 630 eligible patients into this study. The eligible patients were patients with cancer who met the inclusion and exclusion criteria and were scheduled to receive ME or HE chemotherapy.

The study period involved a screening period of 4 to 12 days, a treatment period of 7 days and a follow-up period of 14 days. Eligible patients were randomized in a 1:1 ratio to receive either a Granisetron TDS patch followed by a placebo capsule (Granisetron TDS group) or a placebo patch followed by a Granisetron capsule containing 2 mg granisetron HCl (comparator group).

Up to 2 days before start of chemotherapy, a self-adhesive patch was administered (by study staff or the patient), containing the study drug or placebo, which remained in place for 7 days. The exact number of days of treatment with capsule depended on the duration of the chemotherapy regimen.

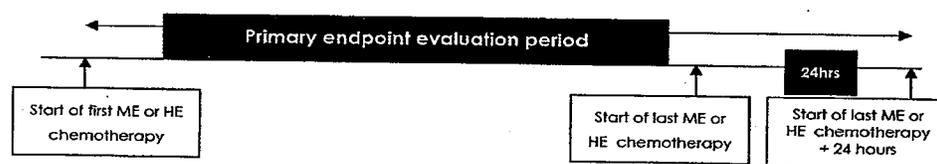
A double-dummy method was used to ensure blinding. Each patient received a patch (active or placebo) and an appropriate number of capsules (active or placebo). The patches containing granisetron and patches without granisetron were of identical appearance, as were the capsules containing granisetron and placebo capsules.

Demographic and baseline characteristics (including medical history, prior and concomitant illness, prior and concomitant medication, physical examination, vital signs, ECG and laboratory values) were documented at Screening. Safety characteristics and clinically relevant changes in vital signs, ECG and laboratory parameters, were documented throughout the study. Efficacy parameters (nausea, vomiting and retching, administration of rescue medication, and patients global assessment) were assessed at Visits 1 to 6 (Study day 1 to Study day 6). On study Day 20 (+2 days), patients returned to the site for a final safety assessment. Vital signs and physical examination changes were compared to Screening assessments.

The primary efficacy endpoint is percentage (%) of patients achieving complete control (CC) of CINV (CC defined as no vomiting and/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 ME or HE chemotherapy regimen.

Figure 3.1.1.1 illustrates the first administration of the ME or HE chemotherapy regimen until 24 hours after the start of the last day's administration of the ME or HE chemotherapy regimen.

**Figure 3.1.1.1 (Applicant's) Diagram for primary endpoint evaluation period**



The secondary efficacy endpoints in this study are:

- Time from start of ME or HE chemotherapy to treatment failure (failure of CC);
- Percentage of patients achieving CR (no vomiting and no rescue medication) of CINV overall and during different time periods;
- Percentage of patients requiring rescue medication;
- Percentage of patients with greater than mild nausea overall and during different time periods;
- Percentage of patients with vomiting/retching overall and during different time periods.

### 3.1.2 Statistical Methodologies

The following populations were defined for the statistical analyses:

- Full analysis set (FAS): all randomized patients who received study treatment (GTDS or active capsule) and had at least one efficacy assessment after the start of chemotherapy. Patients were analyzed according to the actual treatment.
- Per protocol set (PPS): all FAS patients without violations of the protocol which directly impinged on or affected the primary endpoint. These violations were defined prior to the un-blinding of the study. Patients were analyzed according to the actual treatment.
- Safety Set (SS): all patients who received at least one dose of study treatment (GTDS or capsule). Patients were analyzed according to the actual treatment.

The FAS and PPS analyses were performed for the primary efficacy parameter (as the main supportive analysis), secondary efficacy endpoints, demographic data, and baseline characteristics. In addition, the applicant indicated that the analysis of the primary efficacy endpoint on the PPS was considered the primary analysis because this study is a non-inferiority study.

The null hypothesis was that the GTDS is inferior to oral granisetron. The alternative hypothesis was that the GTDS is not inferior to oral granisetron. The hypothesis of non-inferiority was tested via a point estimate of the difference (D) in percentage CC between the two treatment groups, plus a 2-sided 95% confidence interval (CI). If the lower limit of the CI was found to be greater than -15%, then the null hypothesis was rejected. The 2-sided 95% confidence interval of D was obtained via a logistic regression, adjusting for study treatment, gender, planned duration of chemotherapy regimen (3, 4 or 5 days), planned cisplatin/corticosteroid use, and chemotherapy naive status (yes, no) as recorded in IVRS. A main effects model was used.

For the secondary endpoint analysis, Cox's proportional hazards (PH) model were used for time (measured in hours) from start of chemotherapy to failure of CC, time from start of ME or HE chemotherapy to failure of CR, time from start of ME or HE chemotherapy to first administration of rescue. In addition, the applicant applied logistic regression analysis with adjustment of the stratification IVRS (interactive voice response system) variable to compare the treatment effects assessed by the percentages of patients for the following endpoints during different time periods: achieving CC of CINV, achieving CR of CINV, requiring rescue medication, with greater than mild nausea, and with vomiting/retching. Odds ratios and their respective 95% confidence intervals, overall and for each time period, were obtained. This analysis was split by duration of ME or HE chemotherapy (3, 4, 5 days).

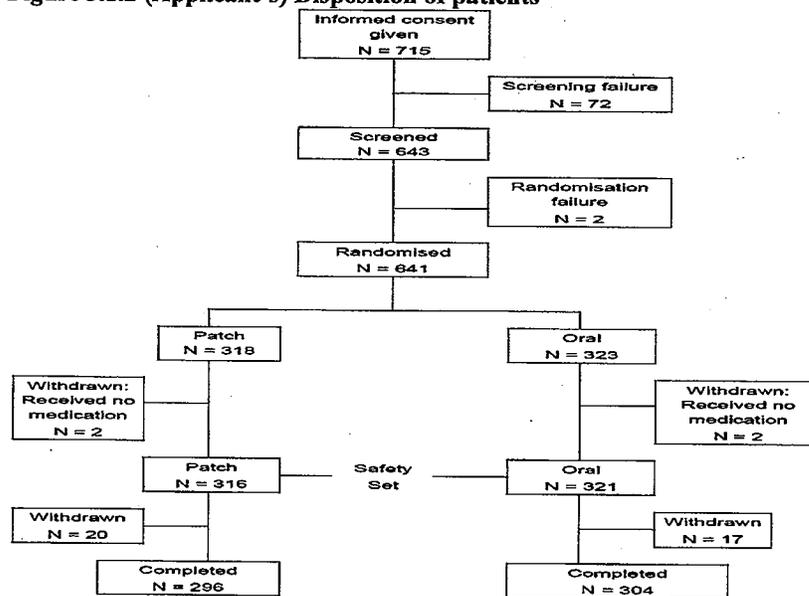
The sample size calculation was based upon the primary efficacy endpoint: the percentage of patients achieving CC of CINV from the first administration until 24 hours after the last administration of ME or HE multi day chemotherapy. The null hypothesis was that the GTDS patch is inferior to oral granisetron. The alternative hypothesis was that the GTDS is not inferior (by greater than a non-inferiority margin of 15%) to oral granisetron. Setting the reference rate

for CC with oral granisetron to 50%, an absolute non-inferiority margin of 15%, and 90% power, 576 patients (288 per group) were required.

### Patient Disposition

A total of 715 patients gave informed consent for this study. Of these, 72 patients were screening failures and 2 patients were randomization failures. Overall a total of 641 patients were randomized in 60 centers in 9 countries. Figure 3.1.2 displayed the disposition of patients while Table 3.1.1 showed the reasons of patients' failures.

**Figure 3.1.2 (Applicant's) Disposition of patients**



N = number of patients

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**Table 3.1.1 (Applicant's) Disposition of patients by reason of failure**

	All	
	n	%
<b>Patients with informed consent</b>	<b>715</b>	
<b>Screening failures</b>	<b>72</b>	<b>10.1</b>
<b>Reason for screening failure</b>		
Withdrawal of consent	25	3.5
Other protocol violation	23	3.2
Violation of inclusion/exclusion criteria	16	2.2
Adverse event(s)	5	0.7
Study terminated by sponsor <sup>1</sup>	3	0.4
<b>Reason for randomisation failure</b>	<b>2</b>	<b>0.3</b>
Violation of inclusion/exclusion criteria	1	0.1
Withdrawal of consent	1	0.1

<sup>1</sup>: Target number of patients was reached; <sup>n</sup>: Number of patients with data available;  
%: Percentage based on number of patients with informed consent.

The applicant indicated that the most common reason for screening failure was withdrawal of informed consent, followed by other protocol violation and violation of inclusion/exclusion criteria. Two patients were recorded as randomization failures, one patient violated the inclusion/exclusion criteria and one patient withdrew consent.

In addition, 20 patients in the GTDS group and 17 patients in the oral group were withdrawn; two additional patients in each group received no study medication. Therefore only 637 patients (316 in the GTDS group and 321 in the oral group) were treated. The reasons for study discontinuation were withdrawal of consent and other protocol violation.

Of the 20 patients in the GTDS group and 17 patients in the oral group, 7 patients in the GTDS group and 3 patients in the oral group had a patch applied, but had taken no capsule. The reasons for withdrawal that applied to more than one patient were insufficient adhesion of patch and AEs. In addition, 13 patients in the GTDS group and 14 patients in the oral group were withdrawn after they had a patch applied and had taken one capsule. In both treatment groups, the most common reasons for withdrawal in these patients were AEs or death of the patient.

Table 3.1.2 displays the number of patients in each of the three patient populations (FAS, PPS, and SS).

**Table 3.1.2 (Applicant's) Analysis sets (All randomized patients)**

	Patch (N = 318)		Oral (N = 323)		All (N = 641)	
	n	%	n	%	n	%
Safety Set (SS) <sup>1</sup>	316		321		637	
Full Analysis Set (FAS)	308	96.9	313	96.9	621	96.9
Per Protocol Set (PPS)	284	89.3	298	92.3	582	90.8

<sup>1</sup>: The numbers of patients are by treatment received; <sup>n</sup>: Number of patients with data available;  
%: Percentage based on number of randomized patients.

Although, based upon Table 7 and the information provided by the section of "Patient Disposition" in the applicant study report, for both patch and oral arms, one can calculate the

number of randomized patients from number of patients completed study, one can not get the number of patients for FAS population from number of patients completed study.

From Table 3.1.2, the applicant indicated that the numbers of patients in the respective analysis sets were comparable between the two treatment groups. A total of 39 patients (24 patients in the GTDS group and 15 patients in the oral group) from the FAS were excluded from the PPS due to protocol violations.

### Demographics and Baseline Characteristics

The applicant indicated that in both the SS and the FAS, age, weight, height and BMI were comparable between the two treatment groups (GTDS and Oral). Around 85% of patients in both treatment groups were older than 40 years. The percentage of male and female patients was comparable between the two treatment groups. In addition, more than three quarters of patients in both treatment groups were White. The remaining patients were mostly Asian and Hispanic/Latino. Finally, the applicant also indicated that the demographic characteristics of the FAS and the PPS were similar to those of the SS.

Demographic data were summarized for SS population in Table 3.1.3.

**Table 3.1.3 (Applicant's) Demography data for Safety Set**

	Patch (N = 316)				Oral (N = 321)				All (N = 637)			
	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range
Age (years)	53.6	12.9	55.0	17-83	55.1	13.5	56.0	16-86	54.4	13.2	55.0	16-86
Weight (kg) <sup>1,2</sup>	66.6	15.6	65.0	31-139	67.8	15.9	65.0	36-134	67.2	15.7	65.0	31-139
Height (cm) <sup>2</sup>	164											
BMI (kg/m <sup>2</sup> ) <sup>1,2</sup>	24.7	5.3	24.2	14.3-51.9	25.2	6.9	24.3	14.2-107	24.9	6.2	24.2	14.2-107
	n		%		n		%		n		%	
<b>Age group</b>												
≤ 40 years	48		15		46		14		94		15	
> 40 years	268		85		275		86		543		85	
<b>Gender</b>												
Male	156		49		158		49		314		49	
Female	160		51		163		51		323		51	
<b>Ethnic origin <sup>3</sup></b>												
White	240		76		251		78		491		77	
Asian	46		15		35		11		81		13	
Hispanic/Latino	30		9		32		10		62		10	
Black/African American	0		0		1		< 1		1		< 1	
Other	0		0		1		< 1		1		< 1	
Non-disclosure	0		0		1		< 1		1		< 1	

<sup>1</sup> Data on weight and BMI were only available for 314 out of 316 patients in the patch group

<sup>2</sup> Includes one patient (patient no. 1081033) with a recorded height of 106 cm and weight of 120 kg (see Appendix C-2, Listing 2.1)

<sup>3</sup> Patients may select more than one ethnic origin

N: Number of patients in the respective treatment group

n: Number of patients

%; Percentage based on N

A summary on nicotine and alcohol use as well as the patients' ECOG performance status were shown in Table 3.1.4.

**Table 3.1.4 (Applicant's) Baseline performance status for Full analysis Set**

	Patch (N = 308)		Oral (N = 313)	
	n	%	n	%
<b>Smoking status</b>				
Smoker	61	20	50	16
Ex-smoker	85	28	78	25
Never smoked	162	53	185	59
<b>Currently on nicotine replacement therapy?</b>				
Yes	0	0	2	1
No	308	100	310	99
Missing	0	0	1	< 1
<b>Current alcohol consumption</b>				
None	214	69	224	72
Monthly	63	20	56	18
Weekly	22	7	28	9
Daily	9	3	5	2
<b>ECOG performance status</b>				
0	123	40	120	38
1	165	54	175	56
2	20	6	18	6

ECOG: Eastern Cooperative Oncology Group;  
N: Number of randomised patients in the respective treatment group;  
n: Number of patients;  
%: Percentage based on N.

Based upon Table 3.1.4, the applicant indicated that the treatment groups were comparable for nicotine, alcohol use, and the patients' ECOG performance status. In both treatment groups, around 55% of patients had never smoked and around 70% of patients currently drank no alcohol. Two patients in the oral group and none in the GTDS group were currently on nicotine replacement therapy.

In addition, for the history of disease therapy, the applicant indicated that the treatment groups were comparable. Twenty percent (20%) of patients in the GTDS group and 21% in the oral group had a history of radiotherapy. The majority of these patients had had one previous course of radiotherapy. Approximately 30% of patients (GTDS group: 28%; oral group: 30%) had a history of chemotherapy. More than 10% of patients in each treatment group had had either 1 or 3 (or more) previous courses of chemotherapy.

### 3.1.3 Applicant's Efficacy Analysis and Conclusion

#### Primary endpoint analysis

The primary efficacy endpoint was the percentage of patients achieving complete control (CC defined as no vomiting and/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 moderate emetogenic (ME) or highly emetogenic (HE) chemotherapy regimen. The primary analysis of the primary efficacy parameter was performed on the PPS. The result of the primary endpoint analysis was summarized in Table 3.1.3.1 for the PPS population

**Table 3.1.3.1 (Applicant's) Primary efficacy endpoint (complete control) analysis result using PPS population**

	Patch (N = 284)		Oral (N = 298)		Adjusted logistic regression <sup>1</sup> Difference (%Yes)	
	n	%	n	%	Estimate	95% CI
<b>Complete Control</b>						
Yes	171	60.2	193	64.8	-4.89	-12.91, 3.13
No	113	39.8	105	35.2		

<sup>1</sup>: Primary comparison estimated via a logistic regression model adjusting for treatment, gender, planned cisplatin and corticosteroid use, planned

regimen duration and chemotherapy naivety as recorded in IVRS.

CI: confidence interval

N: Number of patients in the respective treatment group; n: Number of patients Percentage (%) based on N.

Based upon Table 3.1.3.1, the applicant indicated that the percentage of patients who achieved CC from the first administration until 24 hours after the start of the last day's administration of the ME or HE chemotherapy regimen was comparable between the GTDS and the oral groups with the point estimate of the difference between the GTDS and oral granisetron being -4.89%.

The difference between the 2 treatments was calculated via a logistic regression model adjusting for treatment, gender, planned cisplatin and corticosteroid use, planned regimen duration and chemotherapy naivety as recorded in the IVRS. The lower bound of the 95% confidence interval was -12.91%. Since the lower limit of this confidence interval was above -15%, the null hypothesis was rejected and the alternative hypothesis was accepted, i.e. the GTDS is non-inferior to oral granisetron.

In addition, the applicant indicated that the results of the supportive analysis of the primary endpoint on the FAS were similar to the results obtained for the PPS. The percentage of patients achieving CC was comparable between the two treatment groups.

#### Secondary endpoint analysis

For the analyses of selected secondary endpoints, the applicant indicated that all secondary efficacy analyses were considered as exploratory in nature. Apart from the primary endpoint, no inferiority limits were pre-specified for the other efficacy or safety endpoints. Therefore, due to the exploratory nature of the secondary analyses, no adjustments were made for multiple comparisons.

#### i. Complete control at additional periods

The percentage of patients achieving CC overall and by day is presented in Table 3.1.3.2 for the FAS.

**Table 3.1.3.2 (Applicant's) Percentage of patients achieving complete control overall and by day for Full analysis set**

<b>Planned 3-day course</b>						
	<b>Patch (N = 202)</b>			<b>Oral (N = 201)</b>		
	<b>N*</b>	<b>n</b>	<b>%</b>	<b>N*</b>	<b>n</b>	<b>%</b>
Day 1	200	161	80.5	201	175	87.1
Day 2	199	156	78.4	200	160	80.0
Day 3	198	142	71.7	200	142	71.0
Day 4	174	139	79.9	170	134	78.8
Day 5	163	140	85.9	163	140	85.9
During PEEP	202	123	60.9	201	133	66.2
Overall	182	91	50.0	173	88	50.9
<b>Planned 4/5-day course</b>						
	<b>Patch (N = 106)</b>			<b>Oral (N = 112)</b>		
	<b>N*</b>	<b>n</b>	<b>%</b>	<b>N*</b>	<b>n</b>	<b>%</b>
Day 1	105	89	84.8	112	102	91.1
Day 2	106	84	79.3	112	92	82.1
Day 3	105	81	77.1	112	88	78.6
Day 4	105	79	75.2	112	88	78.6
Day 5	101	79	78.2	107	91	85.1
During PEEP	106	62	58.5	112	72	64.3
Overall	104	58	55.8	108	68	63.0

PEEP: Primary endpoint evaluation period; N: Number of patients in the respective treatment group;  
N\*: Number of patients with data available; n: Number of patients; %: Percentage based on N\*.

Based upon the descriptive analysis shown in Table 3.1.3.2, the applicant indicated that no consistent percentage differences were seen in patients achieving CC between the GTDS and the oral group.

ii. Complete response

The percentage of patients who achieved complete response (CR) is shown in Table 3.1.3.3 for the PPS and FAS.

**Table 3.1.3.3 (Applicant's) Percentage of patients achieving complete response**

<b>Per Protocol Set</b>	<b>Patch (N = 284)</b>		<b>Oral (N = 298)</b>		<b>Adjusted logistic regression<sup>1</sup> Difference (%Yes)</b>	
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>Estimate</b>	<b>95% CI</b>
CR						
Yes	176	62.0	203	68.1	-6.58	-14.43, 1.27
No	108	38.0	95	31.9		
<b>Full Analysis Set</b>	<b>(N = 308)</b>		<b>(N = 313)</b>			
CR	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>Estimate</b>	<b>95% CI</b>
Yes	190	61.7	216	69.0	-7.74	-15.30, -0.18
No	118	38.3	97	31.0		

<sup>1</sup>: Estimated via a logistic regression model, adjusting for treatment, gender, planned cisplatin and corticosteroid use, and planned regimen;  
CI: confidence interval; CR: complete response; N: Number of patients in the respective treatment group; n: Number of patients.

Based upon Table 3.1.3.3, the percentage of patients who achieved CR was higher in the oral group (PPS: 68.1%; FAS: 69.0%) than in the GTDS group (PPS: 62.0%; FAS: 61.7%) for both analysis sets.

iii. Nausea and vomiting episodes

The applicant indicated that the secondary endpoint data for nausea and vomiting by day are affected by the use of rescue medication that may have been taken on previous days. Thus, direct comparison of the treatment groups is not possible. However, these results can be viewed as an intent-to-treat type analysis, taking the study treatment together with any other rescue required as a whole package. Data are presented below by Table 3.1.3.4.

**Table 3.1.3.4(Applicant's) Percentage of patients with vomiting or retching for Full Analysis Set**

Planned 3-day course						
	Patch (N = 202)			Oral (N = 201)		
	N*	n	%	N*	n	%
Day 1	200	32	16.0	201	19	9.5
Day 2	197	31	15.7	200	33	16.5
Day 3	197	45	22.8	200	44	22.0
Day 4	168	20	11.9	170	28	16.5
Day 5	159	12	7.6	162	14	8.6
During PEEP	200	69	34.5	200	54	27.0
Overall	176	76	43.2	170	67	39.4
Planned 4/5-day course						
	Patch (N = 106)			Oral (N = 112)		
	N*	n	%	N*	n	%
Day 1	104	13	12.5	112	5	4.5
Day 2	105	16	15.2	112	18	16.1
Day 3	105	20	19.1	112	18	16.1
Day 4	105	23	21.9	112	19	17.0
Day 5	101	21	20.8	107	14	13.1
During PEEP	104	40	38.5	112	35	31.3
Overall	102	42	41.2	108	35	32.4

N: Number of patients in the respective treatment group;

N\*: Number of patients with data available;

n: Number of patients;

Based upon Table 3.1.3.4, the applicant indicated that for 3 or 4/5 day courses, patients on the GTDS experienced more vomiting and retching on day 1 than those in the oral group. In addition, for the daily and overall differences between the groups, it appeared that patients with vomiting and retching on the GTDS were consistent with the best estimate of 5% more than those on the oral group.

### 3.1.4 Statistical Reviewer's Analysis and Comments

In order to validate the applicant's efficacy claim, this reviewer first performs the following two analyses 1) efficacy comparison by site and 2) simple proportion analysis. Then, I comment on the following two issues: 1) equivalence margin of 15% and 2) single pivotal study.

#### Statistical Reviewer's Analysis

1) Efficacy comparison by site

In order to explore whether the effects of the GTDS non-inferior to oral granisetron were dominated by certain investigator-site, this reviewer calculates the proportions on the complete control for the first 24 hour from the first administration until 24 hours after the start of the last day's administration of the ME or HE chemotherapy regimen (primary endpoint) by investigator-site using PP population. The investigator-site used in this analysis was provided in the data set submitted by the applicant on June 29, 2007.

Since a small site has no capability to dominate the non-inferiority of the study drug GTDS patch to oral granisetron, the proportions of complete control for sites with patients greater than 5 are explored and presented in Table 3.1.4.1.

**Table 3.1.4.1 (Reviewer's) proportions of complete control by site using PPS population**

SITE NUMBER	ORAL		SITE NUMBER	ORAL	
	GRANISTERON	GTDS PATCH		GRANISTERON	GTDS PATCH
Site 10101	77.8 % (7/9)	62.0% (8/13)	Site 10601	90.0% (9/10)	100.0% (8/8)
Site 10103	62.5% (5/8)	80.0% (8/10)	Site 10602	33.0% (2/6)	0.0% (0/2)
Site 10105	81.0% (17/21)	63.0% (12/19)	Site 10603	83.0% (5/6)	100.0% (2/2)
Site 10107	73.0% (11/15)	36.0% (4/11)	Site 10605	67.0% (4/2)	67.0% (2/3)
Site 10108	100% (4/4)	67.0% (2/3)	Site 10608	33.0% (1/3)	50% (2/4)
Site 10109	63.0% (5/8)	90.0% (9/10)	Site 10610	80.0% (4/5)	83.0% (5/6)
Site 10110	79.0% (11/14)	73.0% (11/15)	Site 10612	100.0% (6/6)	100.0% (4/4)
Site 10201	50.0% (4/8)	60.0% (3/5)	Site 10701	0.0% (0/1)	0.0% (0/5)
Site 10203	25.0% (2/8)	60.0% (6/10)	Site 10703	83.0% (5/6)	60.0% (3/5)
Site 10205	0.0% (0/2)	0.0% (0/4)	Site 10706	50.0% (1/2)	83.0% (5/6)
Site 10206	27.0% (3/11)	50.0% (2/4)	Site 10712	33.0% (2/6)	25.0% (2/8)
Site 10207	50.0% (4/8)	46.0% (5/11)	Site 10713	80.0% (4/5)	100.0% (6/6)
Site 10208	72.0% (13/18)	75.0% (9/12)	Site 10809	67.0% (2/3)	67.0% (2/3)
Site 10209	100.0% (2/2)	50.0% (2/4)	Site 10815	50.0% (2/4)	50.0% (1/2)
Site 10210	67.0% (4/6)	60.0% (3/5)	Site 10901	60.0% (3/5)	50.0% (2/4)
Site 10402	46.0% (6/13)	31.0% (5/16)	Site 10903	85.0% (11/13)	73.0% (8/11)
Site 10410	46.0% (5/11)	50.0% (4/8)	Site 10908	50.0% (2/4)	25.0% (1/4)
Site 10411	20.0% (1/5)	33.0% (1/3)	TOTAL	64.8% (193/298)	60.2% (171/284)

Based upon the results from Table 3.1.4.1, for GTDS patch, the proportions of complete control greater (19 sites /35 sites) or less than that in the oral granisetron seems evenly distributed. No particular sites are identified to have unusually large proportions of complete control to dominate the non-inferiority of GTDS patch to oral granisetron.

## 2) Simple proportion analysis

It is noted that the covariate adjustment using the nonlinear logistic model can result in a smaller p-value but a larger variance of the effect estimate compared to the unadjusted analysis. That is, the treatment effect estimate is larger than that produced by unadjusted analysis. As a consequence, in order to explore the credibility of the efficacy for GTDS patch shown by the logistic regression analysis, this reviewer performs a simple analysis of proportions (un-adjusted analysis) on the CC to compare the efficacy of GTDS patch versus oral granisetron. Table 3.1.4.2 presents the result of the efficacy comparison.

**Table 3.1.4.2 (Reviewer's) Simple proportion on the complete control by treatment group (by PPS)**

GTDS PATCH (G) % (n/N)	ORAL GRANISETRON (O) % (n/N)	PERCENT DIF. (G - O)	TWO-SIDED 95% CI OF PERCENT DIF. (G-O)
60.0 (171/284)	65.0 (193/298)	-5.0%	(-12.40%, 3.0%)

CI: confidence interval

N: Number of patients in the respective treatment group; n: Number of patients Percentage (%) based on N.

Table 3.1.4.2 indicates that the lower bound (-12.40%) of the two-sided 95% confidence interval is greater than the negative non-inferiority margin (-15%), indicating that the effect of the GTDS patch is not inferior to that of oral granisetron by 15%. In addition, the result of un-adjusted simple proportion analysis on the complete control is similar to that of the applicant's logistic regression analysis adjusted for treatment, gender, planned cisplatin and corticosteroid use, planned regimen duration and chemotherapy naivety as recorded in IVRS.

In addition, since the results for the non-inferiority analyses provided by the applicant and this reviewer are on the borderline, the non-inferiority of the efficacy for GTDS patch to that for oral granisetron is not supported by substantial evidence, as commented by this reviewer in the following sections. In order to determine if the test drug GTDS patch has efficacy superior to placebo, this reviewer performs the two-sided 95% confidence interval on the complete control rate of GTDS patch using both PPS and FAS patient populations. Table 3.1.4.3 presents the results.

**Table 3.1.4.3 (Reviewer's) 95% two-sided confidence intervals on complete control rate**

Patient Population	GTDS Patch		
	No. Success (n/N)	Success Rate	95% Confidence Interval on Success Rate
PPS Population	171/284	0.60	(0.54, 0.66)
FAS Population	185/308	0.60	(0.54, 0.66)

Table 3.1.4.3 shows the lower bounds for the two-sided 95% confidence intervals on the complete control rate for GTDS patch are 0.54 for both PPS and FAS patient populations. Using the results in Table 3.1.4.3 as a reference, if the medical division deems that the complete control rate of GTDS patch is higher than that of placebo, then, GTDS patch can be considered as effective.

#### Statistical Reviewer's Comments

- 1) Issue on the non-inferiority margin

#### Applicant's response

In the Applicant's November 21, 2007 response to the Agency's Informaton Request regarding the issue of non-inferiority margin of 15%, the applicant indicates that Strakan could not find published data comparing oral granisetron, the reference product directly with placebo in multi-day studies. The only placebo-controlled studies are in single-day chemotherapy, with IV granisetron, as referenced in the protocol and clinical study report for 15C.

In regard with placebo effect, the applicant also cited a research paper reporting a zero complete response rate (defined by the author as the total absence of nausea and vomiting during an entire course of chemotherapy) over 5 days in 70 patients receiving cisplatin-based chemotherapy when treated with prochlorperazine or nabilone. Then, based upon the information from one research paper regarding the complete response rate of placebo, the applicant considers it appropriate to assume that placebo will have a zero complete control rate in the patient population treated in Study 15C.

Then, based upon the above information, the applicant indicates that for the selection of the non-inferiority margin in the protocol, Strakan assumed that the difference in response rates between oral granisetron and placebo was approximately 50% in the multi-day chemotherapy case. However, the applicant also argues that a more formal approach could be applied by calculating the lower 95% confidence limit on the difference of the two response rates (oral granisetron versus placebo). Without presenting raw data, the applicant declares that this confidence interval analysis leads to a more conservative estimate of 39% for the difference between granisetron and placebo, assuming zero control from placebo treated patients. As a consequence, the applicant emphasizes that the non-inferiority margin of 15% is a conservative selection.

Finally, in the conclusion of the applicant's response to the issue of non-inferiority margin, the applicant acknowledges that the limitations for a more formal approach are that:

- There is no direct placebo comparison in the multi-day case;
- The endpoints used were not Complete Control (as in study 15C), but other variations on prevention of nausea and/or vomiting;
- Study 15C was pragmatic in that it included a wide range of MEC/HEC regimens and planned dexamethasone was allowed.

#### Comments on applicant's response

First, it is noted that the applicant could not find published data comparing oral granisetron and placebo assessed by complete control in multi-day studies as defined in the pivotal Study 392 MD/15/C due to the limitations/complexities of the study. The only placebo-controlled studies the applicant cited are in single-day chemotherapy with IV granisetron assessed by complete response (defined as no emesis) as referenced in the protocol and clinical study report for Study 392 MD/15/C. It follows that the duration, day of chemotherapy and the efficacy assessed endpoint for the cited historical studies (IV granisetron) the applicant used to support the selection of non-inferiority margin of 15% were different from that of the pivotal Study 392 MD/15/C (complete control for Study 392 MD/15/C versus complete response for cited historical studies). Thus, the non-inferiority margin of 15% was determined by the applicant based upon the incorrect endpoint, incorrect active control arm (IV instead of Oral), incorrect duration day of chemotherapy (single day instead of multiple days), and zero complete response rate determined from placebo arm not included in the historical trials for active control arm. In other words, the non-inferiority margin of 15% was determined by inadequate information.

In addition, as the applicant admits in their conclusion, the non-inferiority margin of 15% on the difference of proportions of complete control for oral granisetron versus placebo selected was not by a formal statistical approach. On the contrary, the non-inferiority margin of 15% was selected based upon clinical reasoning and exploratory/descriptive type of data analysis using two IV granisetron trials roughly estimating the complete response rate of active control oral granisetron and one research paper quoting placebo effect of zero complete response.

However, as for the non-inferiority margin selection, ICH E10 emphasizes that the margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have as compared with placebo in the setting of the new planned trial. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence. As a consequence, the non-inferiority margin of 15% selected by the applicant without following the recommendations of ICH E10 is debatable. In addition, from the two statistical reviews, dated July 25, 1996 and April 30, 1998, on the IV and oral formulations of granisetron submitted under NDA 20-305, the non-inferiority margin of 10% was used for the non-inferiority analysis. It follows that the non-inferiority margin of 15% selected by the applicant for the pivotal study seems to be too large.

2) Issue on the single pivotal study

One notes that one phase 3 Study 392 MD/15/C and one phase 2 Study 392 MD/8/C were submitted by the applicant to support Granisetron TDS in prevention of nausea and vomiting of moderate or highly emetogenic cancer chemotherapy. However, for the two studies, the objective, inclusion/exclusion criteria, primary assessment period, duration of patch application, duration of chemotherapy application, primary endpoint, and the efficacy analysis method were different. Because of the differences between the two studies (392MD/8/C and 392MD/15/C) noted above, the supportive Study 392MD/8/C is considered as not being able to provide direct support for the pivotal Study 392MD/15/C in prevention of nausea and vomiting of moderate or highly emetogenic cancer chemotherapy.

b(4)

b(4)

As for the efficacy strength provided by the supportive study, the efficacy assessment from the section of "2.1.1 Brief review for Study 392MD/8/C" indicates that no efficacy evidence is shown by the supportive Study 392MD/8/C to support the pivotal Study 392MD/15/C for GTDS in use of the proposed indication. Consequently, the efficacy assessment on the study drug GTDS mainly relies on the single pivotal Study 392 MD/15/C.

First, since the level of evidence for the efficacy of GTDS patch will be judged from the single pivotal Study 392 MD/15/C, this study should be of high quality with substantial demonstration of efficacy as recommended by "the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998". However, both the applicant's logistic regression analysis and this reviewer's simple proportion (un-adjusted) analysis show that the lower bounds of the two-sided 95% confidence intervals for the

proportion of complete control of GTDS patch minus that of oral granisetron are close to the negative non-inferiority margin of 15% (-13.0% and -12.40% respectively for logistic regression and simple proportion analyses). In addition, the estimated CC rate of GTDS patch is 5.0% less than that of oral granisetron. Thus, the borderline result demonstrated by the single pivotal study may indicate that the non-inferiority of the GTDS patch to oral granisetron assessed by the complete control for the acute phase is not robust.

Second, as with the need to show substantial evidence of efficacy in a single superiority study, a single non-inferiority study should also demonstrate a clear clinical efficacy benefit. Consistent with the need for a small p-value in a superiority result, a higher level of confidence can be applied to the usual two-sided 95% confidence interval for the non-inferiority analysis, for example, 99.75%. Following this recommendation, the lower bound of a two-sided 99.75% using the applicant's SAS program for the logistic regression analysis method is -17.0%, less than the applicant's non-inferior margin of -15%, emphasizing/confirming that the non-inferiority of the GTDS patch to oral granisetron assessed by the complete control for the acute phase is not robust under the efficacy criteria required by one single study.

Third, although the complete response (no vomiting and no rescue therapy) was classified as a secondary endpoint by the applicant for this study, it was employed as the primary endpoint by most of drugs used for the proposed indication. For the applicant's analysis on the complete response, Table 3.1.7 indicated that the lower bounds of the two-sided 95% confidence intervals for the proportion of complete response of GTDS patch minus that of oral granisetron are -14.4% and -15.3% respectively for PPS and FAS populations. Because of the two lower bounds either very close (-14.4% from PPS) to or smaller (-15.3% from FAS) than the non-inferiority margin of -15%, the efficacy of GTDS is very likely inferior to that of oral granisetron by more than 15 percent of the complete response rate, even assessed at the regular two-sided 95% confidence interval normally used for two pivotal studies. Since the 15% non-inferiority margin was selected mainly based upon the complete response, the 15% margin is deemed more apt for the efficacy comparison assessed by complete response. Accordingly, the result of the complete response defined as the secondary endpoint by the applicant does not support but diminish the efficacy of GTDS patch in use of the proposed indication.

Finally, as commented previously, the non-inferiority margin of 15% selected without following the recommendation of ICH E10 is debatable and may be too large. However, even with such a large margin, the non-inferiority of GTDS patch to oral granisetron demonstrated by the single pivotal Study 392 MD/15/C shows a borderline result, i.e., the lower confidence bound is very close to the margin. Thus, one may conclude that the single pivotal Study 392 MD/15/C does not provide substantial evidence to support GTDS patch as non-inferior to the oral administration in prevention of nausea and vomiting associated with initial and repeat courses of moderate or highly emetogenic cancer chemotherapy. However, this conclusion does imply the GTDS patch should be judged ineffective in the pivotal study.

### 3.2 Evaluation of Safety for Study 392 MD/15/C

The applicant indicated that the two most common related treatment emergent adverse events (TEAEs) in both treatment groups were constipation (6.6% in GTDS group; 3.1% in oral group), and headache (0.3% in GTDS group; 2.5% in oral group). In addition, six patients in each group were withdrawn due to TEAEs.

Related SAEs were reported for one patient in the GTDS group (severe constipation) and four patients in the oral group (three with Electrocardiogram QT corrected interval prolonged, one with megacolon). Fifteen patients died during the study (7 patients in the GTDS group and 8 patients in the oral group). Of these 15, two died due to post-treatment AEs. One death was assessed as related to study medication. This occurred in the oral group and the underlying AE was megacolon.

This study reported four suspected unexpected serious adverse reaction (SUSARs), three connected with QTc prolongation and one due to megacolon, all in the oral group. Finally, the applicant indicated that the patch was well tolerated in both treatment arms (placebo and GTDS patches). Only one TEAE was reported; this was mild pruritis at the application site.

#### 4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

##### 4.1 GENDER, RACE, AND AGE for Study 392 MD/15/C

In order to assess the consistency of the treatment effect of GTDS patch versus oral granisetron across subgroups, this reviewer performed the subgroup analysis by simple proportion for the primary endpoint complete control using PP patient population. The subgroups analyzed for are Gender (Male and Female), Race (White versus Non-White), and Age group (age  $\leq$  65 and age  $>$  65).

Gender group (Female versus Male)

Table 4.1.1 presents the results of treatment efficacy comparisons for the GTDS patch versus oral granisetron by Gender group (Female versus Male).

**Table 4.1.1.1 (Reviewer's) Proportion difference analysis on overall success by gender using PP population**  
Male Patients

GTDS PATCH (G) % (n/N)	ORAL GRANISETRON (O) % (n/N)	PERCENT DIF. (G - O)	TWO-SIDED 95% CI OF PERCENT DIF. (G-O)
64.0 (88/137)	72.0 (105/145)	-8.0%	(-19.0%, 3.0%)

##### Female Patients

GTDS PATCH (G) % (n/N)	ORAL GRANISETRON (O) % (n/N)	PERCENT DIF. (G - O)	TWO-SIDED 95% CI OF PERCENT DIF. (G-O)
56.0 (83/147)	58.0 (88/153)	-2.0%	(-12.0%, 1.0%)

CI: confidence interval

N: Number of patients in the respective treatment group; n: Number of patients Percentage (%) based on N.

Table 4.1.1 shows that only for Female subgroup, the lower bound of the two-sided 95% confidence interval -12.0% is greater than a negative non-inferiority margin -15%, indicating that the effect of the GTDS patch for female may be non-inferior to that of oral granisetron in the sense of more than 15% complete control rate.

#### Race group (White versus Non-White)

Table 4.1.2 presents the results of treatment efficacy comparisons for the GTDS patch versus oral granisetron by race group.

**Table 4.1.2 (Reviewer's) Proportion difference analysis on overall success by race group using PP population White Patients**

GTDS PATCH (G) % (n/N)	ORAL GRANISETRON (O) % (n/N)	PERCENT DIF. (G - O)	TWO-SIDED 95% CI OF PERCENT DIF. (G-O)
65.0 (142/220)	68.0 (164/240)	-3.0%	(-12.0%, 5.0%)

#### Non-White Patients

GTDS PATCH (G) % (n/N)	ORAL GRANISETRON (O) % (n/N)	PERCENT DIF. (G - O)	TWO-SIDED 95% CI OF PERCENT DIF. (G-O)
45.0 (29/64)	50.0 (29/58)	-5.0%	(-22.0%, 13.0%)

CI: confidence interval

N: Number of patients in the respective treatment group; n: Number of patients Percentage (%) based on N.

Table 4.1.2 shows that only for White sub-group, the lower bound of the two-sided 95% confidence interval -12.0% is greater than the negative non-inferiority margin -15%, indicating that the effect of the GTDS patch for white patients may be non-inferior to that of oral granisetron in the sense of more than 15% complete control rate.

#### Age group (age ≤ 65 and age > 65)

Table 4.1.3 presents the results of treatment efficacy comparisons for the GTDS patch versus oral granisetron by age group.

**Table 4.1.3 (Reviewer's) Proportion difference analysis on overall success by age group using PP population Patients with ages ≤ 65**

GTDS PATCH (G) % (n/N)	ORAL GRANISETRON (O) % (n/N)	PERCENT DIF. (G - O)	TWO-SIDED 95% CI OF PERCENT DIF. (G-O)
56.0 (130/232)	57.0 (128/226)	-1.0%	(-10.0%, 8.0%)

#### Patients with ages > 65

GTDS PATCH (G) % (n/N)	ORAL GRANISETRON (O) % (n/N)	PERCENT DIF. (G - O)	TWO-SIDED 95% CI OF PERCENT DIF. (G-O)
79.0 (41/52)	90.0 (65/72)	-11.0%	(-24.0%, 2.0%)

CI: confidence interval

N: Number of patients in the respective treatment group; n: Number of patients Percentage (%) based on N.

Table 4.1.3 shows that only for the sub-group consisted of patients with ages less than or equal to 65, the lower bound of the two-sided 95% confidence interval -10.0% is greater than the

negative non-inferiority margin -15%, indicating that the effect of the GTDS patch may be non-inferior to that of oral granisetron in the sense of more than 15% complete control rate.

#### 4.2 Other Special/Subgroup Populations

No other special subgroups or populations were analyzed.

### 5.0 SUMMARY AND CONCLUSIONS

#### 5.1 Statistical Issues and Collective Evidence

##### 5.1.1 Study 392 MD/15/C

The following analyses and comments on the efficacy assessments are for the non-inferiority of GTDS patch versus oral granisetron based upon the primary endpoint - complete control for the first 24 hour from the first administration until 24 hours after the start of the last day's administration of the ME or HE chemotherapy regimen. In addition, as commented for Study 392MD/8/C, the supportive Study 392MD/8/C can not provide efficacy evidence to support the pivotal Study 392MD/15/C for GTDS in use of the proposed indication. The efficacy assessment on the study drug GTDS is mainly relied on the single pivotal Study 392 MD/15/C.

- First, based upon the efficacy comparison by investigate-site, for GTDS patch, the proportions of complete control greater (19 sites /35 sites) or less than that in the oral granisetron seems evenly distributed. No particular sites are identified to have unusually large proportions of complete control to dominate the non-inferiority of GTDS patch to oral granisetron when assessed by complete control.
- Second, since the level of evidence for the efficacy of GTDS patch will be judged from the single pivotal Study 392 MD/15/C, this study should be of high quality with substantial demonstration of efficacy as recommended by "the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998". However, both the applicant's logistic regression analysis and this reviewer's simple proportion (un-adjusted) analysis show that the lower bounds of the two-sided 95% confidence intervals for the proportion of complete control of GTDS patch minus that of oral granisetron are close to the negative non-inferiority margin of 15% (-13.0% and -12.40% respectively for logistic regression and simple proportion analyses). In addition, since the complete control rate of GTDS patch is 5.0% less than that of oral granisetron, the borderline result demonstrated by the single pivotal study may indicate that the non-inferiority of the GTDS patch to oral granisetron assessed by the complete control for the acute phase is not robust.
- Third, following the efficacy assessment criteria for the superiority analysis stated in "the Guidance for Industry" regarding the evidence of effectiveness from a single study, in order for the single study to demonstrate a clear clinical efficacy benefit, instead of using 95% two-sided confidence interval for the non-inferiority analysis, a much higher level of two-sided confidence interval is recommended to be applied, for example, 99.75%.

Following this recommendation, the lower bound of the two-sided 99.75% using the applicant's SAS program for the logistic regression analysis method is -17.0% much smaller than the negative non-inferior margin of 15%, emphasizing/confirming that the non-inferiority of the GTDS patch to oral granisetron assessed by the complete control for the acute phase is not robust assessed by the efficacy criteria required by one single study.

- Fourth, although the complete response (no vomiting and no rescue therapy) was classified as a secondary endpoint by the applicant for this study, it was employed as the primary endpoint by most of drugs used for the proposed indication. The applicant's analysis on the complete response indicated that the lower bounds of the two-sided 95% confidence intervals for the proportion of complete response of GTDS patch minus that of oral granisetron are -14.4% and -15.3% respectively, for PPS and FAS populations. Because of the two lower bounds either very close (-14.4% from PPS) to or smaller (-15.3% from FAS) than the negative non-inferiority margin (-15%), the efficacy of GTDS is very likely inferior to that of oral granisetron by more than 15 percent even assessed at the regular two-sided 95% confidence interval normally used for two pivotal studies. Since the 15% non-inferiority margin was selected by the applicant mainly based upon the historical data of complete response, the 15% margin is deemed more apt for the efficacy comparison assessed by complete response. It follows that the result for the complete response analysis does not support but diminish the efficacy of GTDS in use of the proposed indication.
- Finally, the applicant's non-inferiority margin of 15% was selected mainly based upon the endpoint (complete response instead of complete control), active control arm (IV granisetron instead of Oral granisetron), and the duration day of chemotherapy (single day instead of multiple days) different from the current Study 392 MD/15/C, and zero complete response rate determined from placebo arm not included in the historical trials of IV granisetron. The non-inferiority margin of 15% was determined by irrelevant information. In addition, as the applicant admits in their response documents, the non-inferiority margin of 15% on the difference of proportions of complete control for oral granisetron versus placebo selected was not by a formal statistical approach. On the contrary, the non-inferiority margin of 15% was selected based upon clinical reasoning and exploratory/descriptive type of data analysis using two IV granisetron trials roughly estimating the complete response rate of active control oral granisetron and one research paper quoting placebo effect of zero complete response. Consequently, the non-inferiority margin of 15% which was chosen by the applicant without comparing the efficacy of reference drug of oral 2mg granisetron to placebo using historical placebo-controlled trials adequately designed under conditions similar to those planned for the current study (Study 392 MD/15/C) as ICH E10 recommended is disputable. In addition, from the two statistical reviews, dated July 25, 1996 and April 30, 1998, on drug granisetron submitted under NDA 20-305, the non-inferiority margin of 10% was used for the equivalence analysis. It follows that the non-inferiority margin of 15% selected by the applicant for the pivotal study seems to be too large.
- Based upon the above efficacy assessment on the pre-specified non-inferiority study

design, one may conclude that even using this disputable and large margin of 15% selected by the applicant, the non-inferiority of GTDFS patch to oral granisetron demonstrated by the single pivotal Study 392 MD/15/C is only on the borderline and is not robust.

#### 5.1.2 Study 392MD/8/C

- First, due to the following major differences (supportive study vs. pivotal study) between the two studies, the supportive Study 392MD/8/C is considered not being able to provide direct support for the pivotal Study 392MD/15/C in prevention of nausea and vomiting associated with initial and repeat courses of moderate or highly emetogenic cancer chemotherapy: primary endpoint (total control for supportive study vs. complete control for pivotal study), primary assessment period (delayed phase vs. acute phase), duration of patch application (5 days vs. 7 days), duration of chemotherapy application (single day vs. multiple days), efficacy analysis method (superiority vs. non-inferiority).
- Second, as commented in the section of 2.1.1, the non-significant result of the superiority analysis assessed by total control for testing the null hypothesis of no efficacy difference between granisetron TDS patch and oral granisetron only indicates that it is no sufficient data to reject the null hypothesis of no treatment difference. In other word, unable to reject the null hypothesis does not mean that the null hypothesis of no treatment effect difference is true. Accordingly, the non-significant result of testing the null hypothesis of no treatment effect difference does not provide evidence to support the equivalence of the two drugs (granisetron TDS and single oral dose of granisetron).
- Finally, the lower bound (-26%) of the two-sided 95% confidence interval for the proportion difference of complete control in the acute phase for GTDS patch minus oral granisetron is much less than the negative non-inferiority margin of -15% set up for the primary endpoint (complete control for the acute phase) of the pivotal Study 392MD/15/C. It indicates that the efficacy of GTDS patch is inferior to that of oral granisetron by more than 15 percent of complete control.
- In conclusion, based upon above findings, the supportive Study 392MD/8/C is deemed providing no efficacy data to support the pivotal Study 392MD/15/C for the study drug GTDS patch in use of the proposed indication.

#### 5.2 Conclusions and Recommendations

From the statistical perspective, based upon the comments made for the supportive Study 392MD/8/C and the single pivotal Study 392MD/15/C on the efficacy of GTDS patch and the non-inferiority margin of 15% (without statistical sound justification) pre-specified in the protocol, the single pivotal Study 392 MD/15/C does not provide substantial evidence to support GTDS patch in prevention of nausea and vomiting moderate or highly emetogenic cancer chemotherapy.

However, the lower bound for the two-sided 95% confidence interval on the proportions of complete control in the acute phase for GTDS patch is not less than 0.50, calculated using

b(4)

pivotal Study 392 MD/15/C. Using this result as a reference, if the medical division deems that the complete control rate in the acute phase of GTDS patch would be higher than that of placebo, then, GTDS patch can be considered as effective.

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