



HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Preoperative use of granisetron transdermal patch for prevention of postoperative nausea and vomiting (PONV) in patients with history of severe PONV – open label, prospective, pilot study

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1.0 Objectives

1.1 Study Objectives

The objective of the study is to evaluate the efficacy and safety of adding transdermal preparation of granisetron (Sancuso ®) to the current postoperative nausea and vomiting (PONV) standard prophylaxis regimen with dexamethasone and diphenhydramine in patients with the previous history of severe, particularly delayed and/or post-discharge, PONV and undergoing surgical procedure under general anesthesia.

The specific aims of the study include:

1. efficacy of the investigated therapy in prevention of PONV up to 120 hours after surgery
2. incidence and seriousness of the observed side effects
3. ability of patients to self-administer preoperatively and maintain the investigated patch during the perioperative period
4. level of satisfaction with the preoperative PONV prophylaxis.

1.2 Primary Study Endpoints

Number of complete responders (CR, defined as no nausea or vomiting/retching episodes during 120 hours postoperatively, no additional antiemetic medication up to 120 hours after surgery)

1.3 Secondary Study Endpoints

Frequency and severity of nausea and vomiting during the observed period, patient satisfaction scores, length of stay, frequency of re-admission, frequency and type of side effects

2.0 Background

2.1 Scientific Background and Gaps

Postoperative nausea and vomiting (PONV) are common and distressing symptoms to patients. The general incidence of vomiting is about 30%, the incidence of nausea is about 50%, and in a subset of high-risk patients, the PONV rate can be as high as 85%. Unresolved PONV may result in prolonged post anesthesia care unit (PACU) stay and unanticipated hospital admission that result in a significant increase in overall health care costs. The goal of PONV prophylaxis is therefore to decrease the incidence of PONV and thus patient-related distress and reduce health care costs. The major shortcoming of currently used antiemetics is their relatively short duration of prophylactic activity (e.g., about 4-6 hours for all 5HT3 receptor antagonists- 5HT3RA)

requiring its repeated dosing or, for longer acting antiemetics (e.g., scopolamine patch or dexamethasone), the presence of significant side effects and limited effectiveness.

It was reported previously that IV granisetron could be more effective than other 5HT₃RA antiemetics because of its unique metabolic pathways and stronger 5HT₃ receptor affinity. It is therefore important to investigate if the administration of granisetron in the prolonged activity formulation will provide effective antiemetic prophylaxis beyond 24-48 hours after administration.

It is proposed that the non-invasive patch application could extend the available repertoire of the current 5HT₃RAs oral or IV regimens in PONV. Sancuso® was approved by the United States (US) Food and Drug Administration (FDA) in September 2008, and is indicated for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic (HE) chemotherapy regimens of up to 5 consecutive days' duration. The present study will evaluate its effectiveness in the prophylaxis of PONV.

2.2 Previous Data

Granisetron as the hydrochloride (HCl) salt has been approved as an anti-emetic and marketed since the early 1990s. Prior to its approval, a comprehensive development program was conducted and the data submitted for registration. Currently available granisetron formulations (oral and iv) were first marketed in the early 1990s (trade names include Kytril® and Kevtril®). Generic oral and iv granisetron formulations are now available. In the extensive clinical experience gained since, these formulations have proven highly effective in the prevention of CINV, and no post-marketing safety concerns have arisen. Clinical Studies of Sancuso® in CINV (no published work available about its effects in PONV)

- A Phase I PK study (in 6 male and 6 female healthy subjects) demonstrated the delivery of granisetron over 5 days from a 15 cm² TDS applied to the abdomen. Mean maximum observed plasma concentration (C_{max}) was approximately 1.9 ng/ml and the approximate plateau value achieved equated to 1.1 ng/ml (392MD/4/C).
- A Phase I relative bioavailability study (in 12 healthy male subjects) of 4-way cross-over design, compared 3 dosages of Sancuso® (15, 33 and 52 cm²) after a single 6-day application to the upper arm, to that of a 2 mg once-daily oral dose of granisetron for 5 days. Data indicated that average observed plasma concentration (C_{avg}) was reached after 24 hours and maximal concentrations were reached 48 hours after patch application. Based on C_{avg}, a 52 cm² TDS applied for 6 days resulted in a similar plasma concentration to that obtained with once-daily oral dosing of 2 mg granisetron. The pharmacokinetics of granisetron showed dose-proportionality (392MD/11/C).
- A Phase II study (in 175 patients receiving moderately emetogenic (ME) single-day chemotherapy) evaluated efficacy of Sancuso® for the prevention of acute and delayed CINV. Efficacy of Sancuso® in acute emesis was comparable to the reference product, a single oral dose of 2 mg granisetron; in delayed emesis, efficacy was no different from placebo TDS. Sancuso® was well-tolerated (392MD/8/C).
- A Phase III multi-national study (in 637 patients receiving MEC (moderately emetogenic chemotherapy) and HEC (highly emetogenic chemotherapy) multi-day chemotherapy) evaluated the efficacy, tolerability and safety of Sancuso® in prevention of CINV associated with multi-day chemotherapy. The study demonstrated non-inferiority of Sancuso® to oral granisetron in complete control (CC) of nausea and vomiting over the course of multi-day ME or HE chemotherapy (392MD/15/C and Boccia et al, 2010).
- A study to evaluate the skin irritation and sensitization potential of Sancuso® in 212 healthy subjects assessed the cumulative skin irritation and sensitization potential of Sancuso® over a 21-day period. The study concluded that Sancuso® and its matching placebo are slightly irritant when applied on healthy skin, with a lower

number of subjects reporting irritation with the active Sancuso® patch. A low sensitization potential was detected for the active Sancuso® patch. Plasma concentrations in a subset of 24 subjects were assessed following the first patch application, resulting in the apparent dose of the patch of 3.1 mg/24 hours (392MD/26/C).

- A Phase I study in 12 healthy subjects investigated the pharmacokinetics, safety and tolerability of Sancuso® as add-on therapy to iv granisetron. The results from this study indicate that for multiple-day chemotherapy regimens it is possible to administer a single iv dose of granisetron on Day 1 (the same day that the patch is applied) if the patch is not applied 24-48 hours before the start of chemotherapy, allowing granisetron concentrations to achieve target levels immediately on Day 1 without a subsequent effect on the known PK and safety profile of the Sancuso® patch over the following days (392MD/35/C).
- A Phase I study in 12 healthy subjects evaluated the PK and safety profile of the co-administration of iv granisetron and the Sancuso® patch, and the PK profile of repeat Sancuso® patch application. Following combined iv and transdermal administration of granisetron, the plasma concentration vs time profiles exhibited three peak concentrations which reflected the iv administration, the concurrent transdermal patch application, and the subsequent patch application one week later. Sustained mean concentrations of granisetron were observed over the 0 to 24 hours period (with a mean increase between 12 and 24 hours). Peak plasma concentrations relating to transdermal administration of granisetron were achieved approximately 48 hours after each patch application. There was minimal evidence of accumulation following the second transdermal administration of granisetron. Sancuso® was well tolerated when 2 patches were applied consecutively, each for a period of 7 days. Similarly, Sancuso® raised no safety concerns when co-administered with an iv dose of granisetron (392MD/41/C).
- A Phase I study (conducted by Solasia Pharma K.K., Japan) investigated the pharmacokinetics, safety and tolerability of Sancuso® in 12 healthy male Japanese subjects. The PK profile in healthy male Japanese subjects in this study was similar to that seen in a previous study in healthy male non-Japanese subjects. Changes in the clinical safety assessments were unremarkable and the study drug was well-tolerated in healthy Japanese males (SP-0101).
- A Phase I study investigated the effects of Sancuso® on electrocardiogram (ECG) parameters, safety and tolerability compared to placebo and moxifloxacin (positive control) in 240 healthy adult subjects (120 male and 120 female). No clinically significant effect of Sancuso® on ECG parameters was observed (392MD/39/C).
- A Phase I study evaluated the effect of age (Part I) and body mass index (BMI) (Part II) on the pharmacokinetics, safety and tolerability of Sancuso®, each in 30 healthy adult subjects. Quantifiable granisetron concentrations were recorded between 24 and 168 hours post application of Sancuso®. Median time of the maximum observed plasma concentration (t_{max}) values ranged between 60.14 and 72.12 hours across the 5 study groups. No statistically significant differences were reported between the age groups or among the BMI groups for the PK parameters of C_{max} , area under the plasma concentration-time curve between time 0 and the time of last quantifiable sampling point (z) ($AUC [0-z]$), area under the plasma concentration-time curve between time 0 and infinity ($AUC [0-\infty]$) and C_{avg} . It was determined that the continuous variables age, BMI and age*BMI (interaction) have no predicting properties for these parameters (392MD/40/C).
- A Phase I study evaluated the effect of heat on the pharmacokinetics, safety and tolerability of Sancuso® in 8 healthy male and 8 healthy female subjects. Heat was applied using a Cura-Heat® Back & Shoulder pad with a measured local temperature of approximately 42°C (107.6°F). No overall effect of heat on the PK of Sancuso®

2.3 Study Rationale

Clinical guidelines recommend the use of 5HT3RAs in the prevention of PONV and chemotherapy-induced nausea and vomiting (CINV). Granisetron is a potent 5HT3RA, with little or no affinity for other serotonin receptors, or for dopamine-D2, histamine-H1, benzodiazepine and opioid receptors.

Oral and intravenous (iv) formulations of granisetron have been marketed for over 15 years. They are licensed for the prevention of PONV and nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin, which has a strong emetic effect in more than 90% of patients.

ProStrakan, Limited has developed a new granisetron formulation, Sancuso®, a transdermal delivery system (TDS) (granisetron TDS or patch) for the prevention of CINV. Sancuso® consists of a stable matrix of granisetron base (6% w/w) in a commercially-available adhesive (DURO-TAK® 387-2287), designed to sustain delivery of granisetron over a number of days following topical application. Pharmacokinetic evaluation of Sancuso® has indicated that it provides continuous delivery of granisetron over 7 days, providing exposure similar to an oral dose of 2 mg per day (Howell et al, 2009). Previous data indicate prolonged activity of this preparation in prophylaxis of CINV. There is no data available about the efficacy of this formulation in the prophylaxis of PONV.

It should be noted however that there is increasing concern among anesthesiologists and surgeons about patients displaying so called post-discharge (or late) form of PONV. These symptoms occur at least 48-72 hours after the procedure and may last several days (often after patient has been already discharged from the medical facility). It is therefore feasible that the investigated formulation of granisetron will provide prophylactic antiemetic activity throughout the entire period, including acute and delayed phases of PONV.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

- Patients that are between the ages of 18 and 89
- Scheduled to undergo surgical procedures with general anesthesia
- Seen in the anesthesia clinic at least 24 hours before surgery
- History of severe PONV after previous general anesthesia
- Surgical procedures with anticipated duration > 1 hour and no more than 5 hours
- American Society of Anesthesiologists (ASA) physical status I to III

3.2 Exclusion Criteria

- Allergy to granisetron or other 5HT3RA drugs
- Previous allergic reactions to any drug skin patches
- Recent (less than 1 month) or current chemo- or radiotherapy
- Any nausea, vomiting, or retching within 24 hours prior to anesthesia
- Any type of eye surgeries
- History or diagnosis of gastrointestinal obstruction or ileus
- History of serotonin syndrome
- Unable to sign consent

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

- Serious surgical complications during the patch administration preventing in obtaining follow-up results (including re-operation, admission to intensive care unit with intubation, death).
- Inability of patient of keep the transdermal patch for the entire study period (up to

- 120 hours postoperatively)
- Development of allergic reaction or hypersensitivity

3.3.2 Follow-up for withdrawn subjects

Patients will be routinely followed-up for additional 7 days after the patch removal. They will be contacted by phone (if discharged) or visited on the floor (if in the hospital). If discharged, they will be provided with the phone number of the PI and research staff in case of occurrence of any problems.

4.0 Recruitment Methods

4.1 Identification of subjects

Patients will be identified by the anesthesia providers during their anesthesia pre-op visit in the Anesthesia Preoperative Evaluation Clinic (APEC) at Hershey Medical Center (The PI serves as current Medical Director of the Clinic).

4.2 Recruitment process

Patient will be asked about the history of previous general anesthesia and, if there is history of severe PONV (defined as need to administer additional antiemetic medication postoperatively) associated with previous anesthetics, in particular delayed (defined as post-PACU) or post-discharge, the patient will be offered opportunity to enroll into the study protocol.

4.3 Recruitment materials

None will be used. The information about previous history of PONV will be obtained during routine history and physical evaluation in the Clinic.

4.4 Eligibility/screening of subjects

A detailed PONV history will be used to determine occurrence/severity of previous PONV during patient's history and physical evaluation in the Clinic (as it is done anyway for all surgical patients seen in APEC). In general the eligible patients experienced 1 or more episode of PONV with general anesthesia requiring additional treatment in PACU or had episodes of PONV after discharge from PACU or discharge from hospital.

5.0 Consent Process and Documentation

5.1 Consent Process

The informed consent for the study will be obtained in APEC

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Consent to participate will be obtained from eligible patients after preoperative evaluation in the Anesthesia Preoperative Evaluation Clinic (APEC) during the patient's routine preoperative visit.

5.1.1.2 Coercion or Undue Influence during Consent

The patient will be advised that participation in research studies is voluntary and that their decision to participate or not participate will not affect the level of care at this institution.

5.1.2 Waiver or alteration of the informed consent requirement

Not applicable

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

We will obtain a consent form signed by the patient and the person obtaining the consent. An original signed copy will be retained by the patient and the research team and a copy will be placed in the patient's medical record.

5.2.2 Waiver of Documentation of Consent

Not applicable

5.3 Consent – Other Considerations

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

Authorization will be obtained and documented as part of the consent process.

7.0 Study Design and Procedures

7.1 Study Design

This will be an open label, prospective pilot study.

7.2 Study Procedures

Patients will be recruited from the surgical population undergoing preoperative evaluation in Anesthesiology Preoperative Evaluation Clinic at Hershey Med. Ctr. (~15,000 per year). Selected patients (ASA 1-3, N=60) with history of severe PONV after one or more of previous general anesthesia, and scheduled to undergo surgical procedures with general anesthesia will be enrolled into IRB approved protocol. The patch will be placed by the patient at home 24 – 48 hours before surgery as directed by the doctor. The subsequent standardized general anesthesia protocol for elective surgery will include general endotracheal anesthesia with sevofluran, including standard intraoperative PONV prophylaxis (IV dexamethasone and 4 mg and diphenhydramine 25 mg). Postoperative evaluation will include recording of incidence and severity of PONV at the time of discharge from PACU (acute PONV), and at 120 hrs (delayed or post discharge PONV). The final phone interview will be performed 7 days after patch removal in order to capture possible side effects after discontinuation of medication.

7.2.1 Visit 1 - Anesthesia Preoperative Evaluation Clinic and recruitment and drug dispensation

Patient is seen in clinic and identified as having a history of serious PONV, in particular delayed or post discharge PONV. Study will be explained to the patient and consent obtained. The investigational pharmacy will be notified that a study patient has been enrolled and they will prepare the patches for distribution to the patient. EKG will be performed and the results will be recorded preoperatively.

A member of the research team will obtain the assigned patches from the investigational pharmacy and deliver to the anesthesia provider (member of the research team).

The provider will then demonstrate to the patient how to apply the patch and the patient can practice using a placebo patch to show that the correct placement. Patient will then take the actual patch home with them. Patient will also be given a PONV diary to take home with them. Upon returning home from surgery, the patient will be asked to record their instances of nausea and vomiting on a daily basis for up to five days after surgery. At hour 120 post-op, a case manager will telephone the patient and note any recorded

instances of nausea and vomiting since the patient has returned home. The case manager will also check the status of the patch and any medications that were taken as a result of nausea and vomiting. One week after removal of patch (120h post-op + 7 days), a case manager will call the patient a final time to collect adverse events and to assess patient satisfaction with the patch.

7.2.2 Visit 2 - approximately 24-48 hours preoperatively (patient's home)

Patient will apply the patch to their upper arm 24-48 hours before scheduled surgical procedure, as instructed during their pre-op anesthesia visit. The patch will then remain in place until 120 hours after surgical procedure. No backup patch will be provided so the patients with the accidentally missing patch will need to call their primary surgical service for the standard antiemetic medication.

7.2.3 Visit 3- Day of Surgery

Patient will arrive for surgery. A member of the research team will meet them in the SDU and record the time that the patch was applied, and if it has been placed correctly, intact and still in place. Any potential side effects (systemic or local) will be recorded at that time. The subsequent standardized general anesthesia protocol for elective surgery will include general endotracheal anesthesia with sevofluran (no nitrous oxide), muscle relaxants (with reversal), intraoperative IV opioid analgesics, including standard PONV prophylaxis (dexamethasone and [diphenhydramine 25 mg IV](#)).

Early postoperative evaluation will include recording of incidence and severity of PONV at the time of discharge from PACU (acute PONV). The incidence of vomiting or retching will be recorded by the nursing staff. Patients with symptoms requiring a rescue antiemetic—nausea score ≥ 4 on an 11-point Numeric Rating Scale (NRS), retching or vomiting, or patient request—within 6 hours of PACU admission will be given the first line rescue medication promethazine IV 6.25mg as per current standard of care. Promethazine will be used as slow infusion bolus (over 5-10 min) in large, good flowing peripheral IV. If the first line rescue medication does not work the patient will be given ondansetron 4 mg IV). The NRS is an 11-point linear scale on which patients rate their nausea, with 0 meaning no nausea and 10 meaning the worst possible nausea.

The subsequent evaluations will be performed either at the patient's bed (if in the hospital) or by phone call at 120 hrs (delayed or post discharge PONV). The patient will be supplied with a diary to record the information that will be requested on the follow-up phone calls.

The primary efficacy endpoint will be complete response (CR), defined as no emetic episode and no rescue medication; the proportions of patients with no emesis and no additional rescue medication in the 120 hours following the completion of surgical procedure and the change from baseline nausea score using the NRS. Treatment-emergent adverse events (TEAEs), regardless of suspected causal relationship to the study medication, will be also recorded throughout and continued until 5 days after surgery.

7.2.4 Visit 3- Follow-up for possible side-effects

The patient will be contacted by phone to record any possible side-effects they may have experienced since the removal of the patch.

7.3 Duration of Participation

Patient will remain in the study until the final follow-up phone call has been made (7 days

following removal of the patch).

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Granisetron transdermal delivery system - Sancuso®

7.4.2 Treatment Regimen

Study Subjects will receive one patch and it will be applied to the upper arm. The patch will stay in place for 120 hours postoperatively.

7.4.3 Method for Assigning Subject to Treatment Groups

This is an open label study –all study participants will be receiving the patch with the actual medication.

7.4.4 Subject Compliance Monitoring

The presence of the undamaged patch will be confirmed the day of surgery and at the time of discharge.

7.4.5 Blinding of the Test Article

Not applicable

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Patches will be obtained from ProStrakan, LTD. and delivered to the Investigational Pharmacy at Hershey Medical Center.

7.4.6.2 Storage

Stability studies with 15 cm² Sancuso ® patches made at the development site, stored for 6 months at 40°C/75% relative humidity (RH) and for 36 months at 25°C/60% RH have been completed. Stability studies with 52 cm² Sancuso ® patches, made at the development site, using the same adhesive matrix formulation and stored for 24 months at 25°C/60% RH have been completed. Stability studies with 52 cm² Sancuso ® patches, made at the commercial manufacturing site, using the same adhesive matrix formulation and the proposed commercial format have been completed, having reached 6 months storage at 40°C/75% RH and 36 months storage at 25°C/60% and 30°C/65% RH.

Taking into account the stability data available, a shelf life of 36 months is assigned to the finished product. Each individual Sancuso ® patch is supplied in a pouch; it is recommended to store pouches at or below 25°C and out of direct sunlight, although labels for product supplied in the US will currently include the statement “Store at 20 - 25°C (68°-77°F); excursions permitted between 15°- 30°C (59°- 86°F). [See United States Pharmacopeia (USP) Controlled Room Temperature]”.

7.4.6.3 Preparation and Dispensing

Upon enrollment, the PI will write a prescription for the patch and that will be faxed to the pharmacy. The pharmacy will assign a patch to the patient and a member of the research team will pick that up from the pharmacy and deliver it to the anesthesiologist (research team member). The provider will then educate the patient on how to apply the patch to the upper arm

area. The patient will have the opportunity to practice applying the patch using a placebo patch (supplied by the sponsor). The patient will then take the patch home and apply at minimum 24 – 48 hours before surgery as hours (no longer than 48 hours) before surgery.

7.4.6.4 Return or Destruction of the Test Article

The test article will be disposed by the patient to regular waste

7.4.6.5 Prior and Concomitant Therapy

Patient will be on no antiemetic medication at the time of enrollment. After application of the patch each patient will obtain standard PONV prophylaxis in OR consisting of IV dexamethasone 4 mg. and diphenhydramine 25 mg IV. The first line rescue medication will be [Promethazine](#) IV 6.25 mg as per current standard of care. Promethazine will be used as slow infusion bolus (over 5-10 min) in large, good flowing peripheral IV. If this line of rescue medication does not work the patient will receive ondansetron 4 mg IV.

8.0 Data and Specimen Banking For Future Undetermined Research

Not applicable

9.0 Statistical Plan

9.1 Sample size determination

We are planning an open label study of cases treated with granisetron patch (no comparison group, historical control group). Prior data indicate that the failure rate (at least 1 x PONV postoperatively or administration of additional antiemetics) among patients with severe PONV is 0.85. If the true failure rate for experimental subjects is 0.4 (decrease of incidence of PONV by half), we will need to study 60 experimental subjects to be able to reject the null hypothesis that the failure rates for experimental subjects is equal to historical control with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis.

9.2 Statistical methods

The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis.

10.0 Confidentiality, Privacy and Data Management

See attached Research Data Plan Review form

11.0 Data and Safety Monitoring Plan

This is a low risk therapeutic study with an agent with a known safety profile.

11.1 Periodic evaluation of data

The PI and research coordinator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk:benefit ratio to the IRB immediately. A summary of adverse events, study progress

and protocol modifications will be included for IRB review in the continuing review.

11.2 Data that are reviewed

The data to be reviewed will be:

- Safety data
- Untoward events
- Efficacy data

11.3 Method of collection of safety information

Safety information will be collected by the research staff preoperatively and post operatively as described in Section 7.2.

11.4 Frequency of data collection

Data and adverse events assessments begin after the patch is placed on the subject. The research staff will evaluate the subject preoperatively on the day of surgery and then follow postoperatively with a personal or phone interview 120 hours postoperatively when the patch is removed. A second and final phone interview will be performed 7 days after patch removal.

11.5 Individual's reviewing the data

Oversight for the conduct of the study will be provided by the PI and the research coordinator will monitor the data. They will ensure that all eligible criteria and consent requirements are met prior to a subjects' participation in the study and that the procedures and adverse event reporting occur according to the IRB approved protocol.

11.6 Frequency of review of cumulative data

The PI and research coordinator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk:benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review.

11.7 Statistical tests

Not applicable

11.8 Suspension of research

The decision to suspend research will be based on the assessment of all serious adverse events for causality and the decision to stop the trial definitively would be based on the related events that are unexpected and change in frequency of events.

12.0 Risks

12.1 CONTRAINDICATIONS

Sancuso is contraindicated in patients with known hypersensitivity to granisetron or to any of the components of the patch.

12.2 WARNINGS AND PRECAUTIONS

12.2.1 Gastrointestinal

The use of granisetron in patients may mask a progressive ileus and/or gastric distention caused by the underlying condition.

12.2.2 Skin Reactions

In clinical trials with Sancuso, application site reactions were reported that were generally mild in intensity and did not lead to discontinuation of use. The incidence of reactions was comparable with placebo.

If severe reactions, or a generalized skin reaction occur (e.g., allergic rash, including erythematous, macular, papular rash or pruritus), the patch must be removed.

12.2.3 Exposure to Sunlight

Granisetron may be affected by direct natural or artificial sunlight. Patients must be advised to cover the patch application site, e.g. with clothing, if there is a risk of exposure to sunlight throughout the period of wear and for 10 days following its removal because of a potential skin reaction [*see Nonclinical Toxicology (13.3)*].

12.2.4 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT₃ receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT₃ receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT₃ receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Sancuso and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Sancuso and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Sancuso is used concomitantly with other serotonergic drugs.

12.2.5 External Heat Sources

A heat pad should not be applied over or in vicinity of Sancuso patch. Patients should avoid prolonged exposure to heat as plasma concentration continues increasing during the period of heat exposure

12.3 ADVERSE REACTIONS

12.3.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of Sancuso was evaluated in a total of 404 patients undergoing chemotherapy who participated in two double-blind, comparator studies with patch treatment durations

of up to 7 days. The control groups included a total of 406 patients who received a daily dose of 2 mg oral granisetron, for 1 to 5 days.

Adverse reactions occurred in 8.7% (35/404) of patients receiving Sancuso and 7.1% (29/406) of patients receiving oral granisetron. The most common adverse reaction was constipation that occurred in 5.4% of patients in the Sancuso group and 3.0% of patients in the oral granisetron group.

Table 1 lists the adverse reactions that occurred in at least 3% of patients treated with Sancuso or oral granisetron.

Table 1: Incidence of Adverse Reactions in Double-Blind, Active Comparator Controlled Studies in Cancer Patients Receiving Chemotherapy (Events \geq 3% in either group)

Body System Preferred Term	Sancuso TDS N=404 (%)	Oral granisetron N=406 (%)
Gastrointestinal disorders		
Constipation	5.4	3.0
Nervous system disorders		
Headache	0.7	3.0

5-HT₃ receptor antagonists, such as granisetron, may be associated with arrhythmias or ECG abnormalities. Three ECGs were performed on 588 patients in a randomized, parallel group, double-blind, double-dummy study: at baseline before treatment, the first day of chemotherapy, and 5 to 7 days after starting chemotherapy. QTcF prolongation greater than 450 milliseconds was seen in a total of 11 (1.9%) patients after receiving granisetron, 8 (2.7%) on oral granisetron, and 3 (1.1%) on the patch. No new QTcF prolongation greater than 480 milliseconds was observed in any patient in this study. No arrhythmias were detected in this study.

Adverse reactions reported in clinical trials with other formulations of granisetron include the following:

Gastrointestinal: abdominal pain, diarrhea, constipation, elevation of ALT and AST levels, nausea and vomiting

Cardiovascular: hypertension, hypotension, angina pectoris, atrial fibrillation and syncope have been observed rarely

Central Nervous System: dizziness, insomnia, headache, anxiety, somnolence and asthenia

Hypersensitivity: rare cases of hypersensitivity reactions, sometimes severe (e.g. anaphylaxis, shortness of breath, hypotension, urticaria) have been reported

Other: fever; events often associated with chemotherapy have also been reported: leucopenia, decreased appetite, anemia, alopecia, thrombocytopenia.

12.3.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Sancuso. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General Disorders and Administration Site Conditions: Application site reactions (pain, pruritus, erythema, rash, application site irritation, vesicles).

Cardiac Disorders: bradycardia, chest pain, palpitations, sick sinus syndrome

12.4 DRUG INTERACTIONS

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system *in vitro*. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs. However, in humans, granisetron hydrochloride injection has been safely administered with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with antiemetic treatments. Granisetron hydrochloride injection also does not appear to interact with emetogenic cancer therapies. In agreement with these data, no clinically relevant drug interactions have been reported in clinical studies with Sancuso.

Because granisetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP1A1 and CYP3A4), inducers or inhibitors of these enzymes may change the clearance and hence, the half-life of granisetron. In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by granisetron hydrochloride *in vitro*. In *in vitro* human microsomal studies, ketoconazole inhibited ring oxidation of granisetron hydrochloride. However, the clinical significance of *in vivo* pharmacokinetic interactions with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous granisetron hydrochloride. The clinical significance of this change is not known.

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT₃ receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs).

12.5 Loss of confidentiality

There is a possible risk of loss of confidentiality, however we will take every precaution to protect your private health information.

13.0 Potential Benefits to Subjects and Others

13.1 Potential Benefits to Subjects

Patients enrolled into the study might experience less PONV (in particular delayed and post-discharge) postoperatively

13.2 Potential Benefits to Others

This study may lead to an effective option to PONV therapy in the future.

14.0 Sharing Results with Subjects

Results will not be shared with the study subjects.

15.0 Economic Burden to Subjects

15.1 Costs

There are no additional costs to the study subjects to participate in this study.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Number of Subjects

We require 60 evaluable patients, with an enrollment of up to 80 patients which would include a potential of 20 screen failures.

17.0 Resources Available

17.1 Facilities and locations

Hershey Medical Center, Hershey, PA

17.2 Feasibility of recruiting the required number of subjects

Patients will be recruited from the surgical population undergoing preoperative evaluation in Preoperative Evaluation Clinic at Hershey Med. Ctr. (~15,000 per year)

17.3 PI Time devoted to conducting the research

PI is the Medical Director of APEC

17.4 Availability of medical or psychological resources

Not applicable

17.5 Process for informing Study Team

Meetings will be held periodically as needed to ensure all research team members are informed about the protocol and their duties. Team emails will be used to keep team members up to date on study progress and modifications.

18.0 Other Approvals

Approvals will be received from ProStrakan and the FDA (IND)

19.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Not applicable

20.0 Multi-Site Research

Not applicable.

21.0 Adverse Event Reporting

21.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than “adverse reaction”. <ul style="list-style-type: none"> • <i>Reasonable possibility.</i> For the purpose of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

21.2 Recording of Adverse Events

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator. All adverse events (including those labeled) will be recorded in each patients Case Report Form and evaluated for relationship to study drug, severity, date of onset, date of resolution and outcome.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

Note: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study

The test finding is considered an adverse event by the investigator.

21.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

21.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

21.4.1 Written IND Safety Reports

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

21.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

21.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

21.6 Reporting Adverse Reactions and Unanticipated Problems to ProStrakan, Ltd.

The investigator will also provide ProStrakan with a copy of the FDA form 3500A completed for all serious adverse events. The information will include the investigator's assessment of causality. This information will be sent to the Company within 10 days of receipt of the adverse event reported by the investigator. A copy of the completed FDA 3500A form submitted to the FDA will be sent to Drugsafety@prostrakan.com. The company will enter all safety information in the Global Safety Database along with the investigator's assessment of relationship of the event to the study medication. Any follow up information will also be sent to the Company within 10 days of receipt of the information by the Investigator on a completed FDA 3550A form. The investigator agrees to respond to questions from the Company regarding reports of serious adverse events and for clarification of adverse event information submitted.

21.7 Unblinding Procedures

Not applicable

21.8 Stopping Rules

The decision to suspend research will be based on the assessment of all serious adverse events for causality and the decision to stop the trial definitively would be based on the related events that are unexpected and change in frequency of events.

22.0 Study Monitoring, Auditing and Inspecting

22.1 Study Monitoring Plan

22.1.1 Quality Assurance and Quality Control

The protocol data will be recorded on data collection forms by trained research staff via participant interview, telephone survey, and electronic medical record abstraction. The participant will complete a paper daily diary. The data will be double-data entered into REDCap (Research Electronic Data Capture application) in a timely fashion. Data validation error checks will be programmed into REDCap to minimize the entry of erroneous data. Data entry discrepancies will be reviewed and resolved by a Clinical

Research Coordinator.

Data monitoring will be conducted by Data Management staff in the Department of Public Health Sciences. During the monitoring visits the PHS staff will verify the presence of all essential and regulatory documents, review the participant informed consents, perform source document verification, confirm the eligibility criteria for all participants, audit the accuracy of data stored in REDCap against the data collection forms, compare adverse events and concomitant medications recorded against the electronic medical record, ensure that all protocol deviations/violations are recorded, determine the timeliness of data entry, and ensure that all data errors have been resolved.

The initial data monitoring visit will occur after five participants have completed the study. The frequency of monitoring will continue to be evaluated based upon previous findings, protocol changes, changes in the research team, or indications of poor data quality or participant safety issues.

22.1.2 Safety Monitoring

The Principal Investigator will confirm that all adverse events (AE) are correctly recorded on the AE data collection forms by the research coordinators; be available to answer any questions that the research coordinators may have concerning the AEs; and will notify the IRB, FDA, sponsor, Company and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the study.

The research coordinators will complete the appropriate AE forms and assist the Principal Investigator in preparing reports to the IRB, FDA, Company and/or DSMB of all Unanticipated Problems/Serious Adverse Events (SAEs).

The Public Health Sciences Data Monitoring staff will confirm that the AEs are correctly recorded on the data collection forms and entered into the REDCap database. The monitor will confirm that the AEs are consistent with the source documents are reported to the appropriate regulatory bodies in the timeframe required.

23.0 References

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24.0 Appendix