# Effects of Rolapitant on Nausea/vomiting in Patients with Sarcoma Receiving Multi-day Highly Emetogenic Chemotherapy (HEC) with Doxorubicin and Ifosfamide Regimen (AI)

## 1.0 Objectives

**Primary Objective:**

To evaluate the effect of Rolapitant on nausea/vomiting in patients with sarcoma receiving multi-day HEC regimen of Doxorubicin and Ifosfamide (AI).

**Secondary Objectives:**

(1) To evaluate the toxicity of Rolapitant in patients receiving AI regimen.
(2) To evaluate the effects of Rolapitant on patient reported outcomes.

## 2.0 Background

### 2.1 Chemotherapy-induced Nausea and Vomiting (CINV)

Nausea and vomiting are one of the most debilitating side effects of cytotoxic chemotherapy. CINV is a frequent adverse event that can impair the quality of life in cancer patients (1, 2). The time course of CINV is well recognized for single-day chemotherapy regimens. It may persist for several days and has frequently been classified as having an acute phase (starting within 24 hours of the chemotherapy administration) and a delayed phase (starting approximately 16-24 hours after initiation of chemotherapy and lasting to approximately 120 hours post-chemotherapy). There are both acute (0 to 24 hours) and delayed phases of CINV which are distinct after HEC but less differentiated after MEC. Active management of CINV reduces patient suffering and increases the likelihood that cancer patients will continue to receive potentially life-saving treatment at appropriate doses.

### 2.2 Prevention/Treatment for CINV

CINV is triggered by multiple factors involving patients' characteristics and type of chemotherapy regimen. Several neurotransmitters, located in the gastrointestinal (GI) tract or in the central nervous system (CNS), are involved with the pathophysiology of CINV, triggering the emetic center located in the medulla (3). These include histamine, acetylcholine, serotonin, dopamine, and substance P (4-7). The acute phase, the first 24 hrs following chemotherapy treatment, is mediated largely by chemotherapy-induced increases in serotonin (5-HT3) release and activation of 5-HT3 receptors on vagal afferent neurons in the gut. 5-HT3 receptor antagonists (5-HT3RA) are clinically effective in preventing acute CINV, particularly when given in combination with corticosteroids such as dexamethasone (8).

Delayed CINV occurs from 2 to 5 days after chemotherapy and has a different etiology than acute CINV (9). Antiemetic therapy with a corticosteroid and 5-HT3RA, particularly with the first generation 5-HT3RA, is less effective during the delayed as compared to

the acute phase of CINV. The primary etiology of delayed CINV appears to involve the release of the neurokinin peptide substance P in the brainstem. When an NK1 antagonist, 5-HT3RA, and corticosteroid are given in combination, there is a greater reduction in CINV compared to that seen with the use of the combination of a 5-HT3RA antagonist and corticosteroid alone. The NK1 receptor antagonist aprepitant was approved by the FDA and by the EMA for the prevention of acute and delayed CINV associated with HEC, including high-dose cisplatin, and MEC when used in combination with a 5-HT3RA and corticosteroids (10). Although aprepitant and fosaprepitant (iv formulation) are effective, dosage adjustment of other concomitantly administered drugs is necessary because aprepitant is a mixed inducer/inhibitor of cytochrome P450 (CYP) 3A4 and also affects other CYP enzymes. Furthermore, aprepitant requires several doses during each cycle of chemotherapy (11-14).

**2.3 CINV in Sarcoma Patients Receiving AI regimen**

AI is multi-day regimen of highly emetogenic chemotherapy, with high incidence of delayed CINV. Fosaprepitant, NK1 receptor antagonist (RA), administered IV as single dose is FDA-approved, in combination with 5HT3RA and dexamethasone has improved the control of emesis. However, delayed N/V still remains problematic (9). We, therefore investigated the effects of fosaprepitant administered IV on day 1 vs days 1 and 4 on CINV and the effect on ifosfamide (Ifex) and its active metabolites, due to potential drug interactions via CYP450. Patients planned to receive AI, were randomized 1:1 to Arm A (single- dose fosaprepitant on day 1) or Arm B (2-doses, on days 1 and 4). Blood samples were drawn for levels of Ifex/metabolites to be analyzed at the end of study. All patients could receive 2 doses during cycles 3-6. Pts were monitored for N/V with daily symptom diary and FLIE (functional living index -- emesis) score (days 1, 5 and 10). 40 eligible pts were randomized. Fosaprepitant administered as 2 doses resulted in significantly better control of delayed N/V as compared to single-dose or the control cycle (response rate 10% and 17% vs 50%, respectively) (15, 16). Fosaprepitant had minor effects on Ifex and metabolites levels, which was partly compensated by autoinduction.

**2.4 Rolapitant, A New NK-1 Receptor Antagonist**

Rolapitant (formerly referred to as SCH 619734) is a potent, selective, competitive neurokinin-1 (NK1) receptor antagonist with no known activity at other pharmacologic targets (17). It binds with high affinity to the human NK1 receptor (Ki = 0.66 nM) and competitively antagonizes functional effects mediated by activation of the NK1 receptor in cultured cells (Kb = 0.45 nM). The endogenous activator of NK1 receptors is the neuropeptide Substance P (18). Rolapitant does not have significant affinity for NK2 or NK3 receptors or for a battery of other receptors, transporters, enzymes, and ion channels. The compound is active in animal models of CINV and has demonstrated efficacy in Phase 2 studies in patients receiving HEC. Rolapitant has been free of clinically relevant drug interactions in studies conducted to date, has rapid and good brain penetration which may contribute to its quick onset of action, and a long half-life that allows for dosing only once during each cycle of chemotherapy. PET occupancy studies as well as clinical efficacy data support the use of only a single dose of rolapitant to protect patients for 5 days from CINV (19, 20).

### 2.4.1 Preclinical Studies

Rolapitant has been evaluated in a series of non-clinical toxicity studies of up to 6 months duration in rats and up to 9 months duration in monkeys by oral administration and up to 14 days duration in rats and up to 1 month duration in monkeys by intravenous (IV) infusion. Developmental and reproductive toxicity studies, genetic toxicity studies, and safety pharmacology studies were also conducted. In addition, genetic toxicity studies and a safety pharmacology study were conducted with the pharmacologically active metabolite SCH 720881 (M19). Furthermore, 2-year oral carcinogenicity studies of rolapitant in rats and mice have been completed.

The major findings in the non-clinical toxicity studies reported to date are convulsions in rats, mice, and monkeys at high lethal or near lethal doses (oral administration) and in monkeys (after IV infusion) as well as developmental and reproductive findings in female rats. For convulsions, exposure margins have been identified in the non-clinical species relative to clinical exposure data at an oral dose of 180 mg and there has been no evidence of treatment-related seizures in the completed clinical trials. Since the rolapitant clinical development program has not nor will include women who are pregnant or attempting to become pregnant, the findings in the developmental and reproductive studies in rats are not considered relevant for the clinical trials in CINV. The mouse carcinogenicity study with rolapitant was negative; the rat carcinogenicity study showed a non-significant increase in thyroid follicular cell tumors and benign adrenal medullary tumors.

To evaluate the IV administration of rolapitant in humans, blood compatibility and local tolerance studies were also performed. The results from the in vitro blood compatibility study as well as animal studies indicate that the intended clinical formulation does not cause hemolysis in human, rat or monkey blood. The local tolerance study showed that the intended formulation is well tolerated when administered by either the intended IV route or potential misdose routes. Additionally, results obtained from the 14-day IV rat, 14-day IV monkey and one-month IV monkey studies indicate rolapitant is well tolerated at 20 mg/kg/day in rats and up to 15 mg/kg/day in monkeys. These results also indicated that the solubilizing agents in the rolapitant IV formulation are well tolerated at 10 mL/kg when administered at the defined concentration, approximately 5-fold higher than the maximal infusion volume (1.58 mL/kg, 95 mL/60 kg human) anticipated clinically.

### 2.4.2 In vivo Activity of Rolapitant

Ferrets have proven to be a useful animal model of chemotherapy-induced emesis, and have been used extensively to demonstrate the antiemetic effects of drugs, including NK1 receptor antagonists like aprepitant. Rolapitant produced a dose-dependent inhibition of retching and vomiting with an ED50 of 0.07 mg/kg when dosed orally to ferrets 4 hrs prior to cisplatin treatment. Moreover, a single 1 mg/kg oral dose of rolapitant given 4 hrs prior to cisplatin substantially inhibited both the acute and delayed retching and vomiting for 72 hrs. Cisplatin-induced retching and vomiting was also

completely abolished (ca. >95%) by once daily oral administration of 1 mg/kg of rolapitant for 3 days after cisplatin treatment.

In conclusion, the IV and oral monkey studies have shown that the safety profile of rolapitant is similar at the NOAEL/maximum tolerated dose following administration of rolapitant by either the IV or oral route of administration. Moreover, the systemic toxicity profiles and exposure levels are comparable between IV and oral administrations at these dose levels.

**2.4.3 Clinical Experience**

The total number of subjects exposed to oral rolapitant is approximately 2,800, which includes 1,567 CINV patients and 1,231 healthy volunteers or patients from several additional Phase 1 and Phase 2 studies (21). Rolapitant was well tolerated at single doses up to 800 mg or as a once-daily dose up to 50 mg for 10 days. Orally administered rolapitant was completely bioavailable, rapidly absorbed, and slowly cleared. Maximum concentrations of a 200 mg dose were approximately 1000 ng/mL and were achieved by approximately 4 hrs. The half-life was approximately 170 hrs (average), suggesting that a single dose may be sufficient to prevent CINV during both the acute and delayed phases of CINV. Rolapitant is highly bound to plasma proteins, with an unbound (free) fraction of <1%. Urinary excretion of the dose is minor, and the major route of elimination is via the feces. Rolapitant is extensively metabolized by oxidation, primarily to M19, an equipotent human NK1 receptor antagonist. The formation and elimination of M19 are slow.

In Phase 1 drug interaction studies, administration of rolapitant did not alter the pharmacokinetics of midazolam, dexamethasone or ondansetron, drugs metabolized by cytochrome P450 3A4. This indicates lack of a clinically relevant inhibition of CYP3A4 by rolapitant. Moreover, the PK of repeated doses of dexamethasone was also unaffected by a single 200 mg (equivalent to the 180 mg free base dose in the treatment section) oral dose of rolapitant, indicating a lack of significant CYP3A4 induction by rolapitant or its metabolite. Inhibition of CYP3A4 by concomitant agents is unlikely to affect the PK of single doses of rolapitant, since concentrations of both rolapitant and the active metabolite M19 were unaffected by repeated daily oral doses (400 mg) of the potent CYP3A4 inhibitor ketoconazole.

In a recently conducted drug interaction study to assess the effect of rolapitant on the pharmacokinetics of specific probe substrates, preliminary results indicate that rolapitant increased the PK exposure of dextromethorphan, a CYP2D6 substrate, digoxin, a P-gp substrate, and sulfasalazine, a BCRP substrate suggesting that rolapitant is a moderate inhibitor of CYP2D6 and an inhibitor of P-gp and BCRP. Therefore, dosage adjustments may be warranted for sensitive CY2D6 substrates and/or P-gp, BCRP transporter substrates when given concomitantly with rolapitant. However, Rolapitant did not alter the

pharmacokinetics of tolbutamide, omeprazole, efavirenz or repaglinide, drugs metabolized by CYP2C9, CYP2C19, CYP2B6, or CYP2C8 respectively.
In a recently conducted PK study in subjects with impaired hepatic function, preliminary results indicate comparable rolapitant PK profiles were observed in subjects with mild hepatic impairment and a slight decrease in exposure with subjects with moderate hepatic impairment when compared to healthy subjects. Therefore, dose adjustment for rolapitant when administered to patients with mild to moderate hepatic impairment is not required. Subjects with severe hepatic impairment were not evaluated in this study.

A human ECG study demonstrated no effects of rolapitant 200 mg or 800 mg (4 times the therapeutic dose) on the QTc interval. A clinical PET study demonstrated that single oral doses of rolapitant ranging from 5 to 200 mg can block the occupancy of cortical NK1 receptors by the selective PET ligand 11C-GR205171. After a 200 mg dose, over 90% of central NK1 receptors remained blocked for at least 5 days.

The results from the dose range-finding study showed rolapitant administered as a single dose of 200 mg with a 5-HT3 receptor antagonist and dexamethasone to be highly effective in the prevention of CINV following HEC, together with data from the Phase 1 PET study, led to the dose selection and design of three global multicenter, randomized, parallel-group, double-blind, active-controlled Phase 3 studies conducted in subjects receiving HEC (P04832 and Study P04833) and in subjects receiving MEC (Study P04834).

These studies were designed to evaluate the efficacy of a single dose of rolapitant 200 mg administered orally with granisetron and dexamethasone compared to placebo administered with granisetron and dexamethasone for the prevention of delayed phase CINV (>24 to 120 hours). The primary endpoint of all three studies was achieved (21-24). Specifically, the proportion of subjects who had no emesis and no use of rescue medication during the delayed phase of CINV, >24 through 120 hours following initiation of HEC or MEC, was significantly higher for subjects receiving rolapitant compared with subjects receiving placebo (71.4% vs. 60.9%, respectively, $p < 0.001$). Likewise, the proportion of subjects who had no emesis and no use of rescue medication was significantly higher for subjects receiving rolapitant compared with subjects receiving placebo during the acute phase (< 24 hours) (83.5% vs. 78.7%, respectively, $p = 0.003$) and during the overall phase (0-120 hours) (68.7% vs. 58.1%, respectively, $p < 0.001$). Multiple secondary and tertiary endpoint comparisons favored the rolapitant group in the individual studies and in the pooled analyses and contribute additional support for the benefit of rolapitant during the delayed, acute and overall at risk period (0 to 120 hours) for patients receiving emetogenic chemotherapy. In addition, rolapitant was safe and well tolerated. No AEs were clearly attributable to administration of rolapitant, and neurological and other clinical and laboratory examinations did not detect specific safety signals that could be ascribed to rolapitant.

### 2.4.4 Drug Interaction

#### 2.4.4.1 Effect of Rolapitant on Other Drugs

Rolapitant is not an inhibitor nor an inducer of CYP3A4. Therefore, no dosage adjustment for dexamethasone (CYP3A4 substrate) is needed when co-administered (25).

Rolapitant is a moderate CYP2D6 inhibitor, an inhibitor of Breast-Cancer-Resistance Protein (BCRP) and an inhibitor of P-glycoprotein (P-gp).

CYP2D6 Substrates with a Narrow Therapeutic Index: Increased plasma concentration of CYP2D6 substrates may result in potential adverse reactions. A three-fold increase in the exposure of dextromethorphan, a CYP2D6 substrate, was observed 7 days after a single dose of Rolapitant. The duration of CYP2D6 inhibition was not studied beyond 7 days and may last longer. Concomitant use with thioridazine is contraindicated. Avoid use of Rolapitant with pimozide. Monitor for adverse reactions if concomitant use with CYP2D6 substrates with a narrow therapeutic index cannot be avoided (25).

BCRP Substrates with a Narrow Therapeutic Index (e.g., methotrexate, topotecan, or irinotecan): Increased plasma concentrations of BCRP substrates may result in potential adverse reactions. Monitor for adverse reactions related to the concomitant drug if use of Rolapitant cannot be avoided. Use the lowest effective dose of rosuvastatin.

P-gp Substrates with a Narrow Therapeutic Index: Increased plasma concentrations of digoxin, or other P-gp substrates, may result in potential adverse reactions. Monitor for increased digoxin concentrations. Monitor for adverse reactions if concomitant use of Rolapitant with other P-gp substrates with a narrow therapeutic index cannot be avoided (25).

#### 2.4.4.2 Effect of Other Drugs on Rolapitant

Strong CYP3A4 Inducers (e.g., rifampin): significantly reduced plasma concentrations of rolapitant can decrease the efficacy of Rolapitant; avoid use of Rolapitant in patients who require chronic administration of such drugs (25).

### 2.4.5 Rationale for the Study

The NK1 antagonist aprepitant was approved by the FDA and by the EMA for the prevention of acute and delayed CINV associated with HEC, including high-dose cisplatin, and moderately emetogenic chemotherapy (MEC) when used in combination with a 5-HT3 antagonist and corticosteroid. Although aprepitant is effective, dosage adjustment of concomitantly administered drugs is necessary because aprepitant is a mixed inducer/inhibitor of cytochrome P450 (CYP) 3A4 and also affects other CYP enzymes. Furthermore, aprepitant requires several doses during each cycle of chemotherapy. Rolapitant has been free of clinically

relevant drug interactions in studies conducted to date, has rapid and good brain penetration which may contribute to its quick onset of action, and a long half-life that allows for dosing only once during each cycle of chemotherapy. PET occupancy studies as well as clinical efficacy data support the use of only a single dose of rolapitant to protect patients for 5 days from CINV. AI is a highly emetogenic regimen with the potential for improvement in delayed nausea/vomiting with rolapitant in addition to 5HT3RA and steroids.

### 2.4.6 Study Update

To date, 28 patients have been enrolled on to this study, all of them have completed more than 1 cycle of treatment. The treatment of Rolapitant is well tolerated. In the first cohort- Cohort 1 (dexamethasone 12 mg on day 1, and 8 mg on days 2-5), none of the 9 patients had complete response in days 1-10. Since there is no interaction between Rolapitant and CYP3A4, the amendment 2 was written to keep the dose of dexamethasone constant at 12 mg on Days 2-5 for Part 1 (Rolapitant). In this new cohort- Cohort 2 (dexamethasone 12 mg on days 1-5), the complete response rate (no emetic episodes and no rescue medications) was 29% (5/19) in days 1-10; and the complete response rate was 32% (6/19) for emetic episodes only related to chemotherapy. We therefore would like to expand our experience with the current regimen to confirm the response rate prior to initiation of Part 2 of the study.

## 3.0 Background Drug Information

### 3.1 Rolapitant

For this trial, Rolapitant will be supplied by TerSera as investigationally-labelled commercial supply.

### A. Physical Description of Study Drug

Rolapitant will be provided as Rolapitant, 90 mg, (equivalent to 100 mg rolapitant hydrochloride monohydrate) tablets for oral administration. Tablet appearance is blue modified capsule shaped tablet debossed on one side with T0101 and 100 on the other.

### B. Packaging, labeling, and Storage

The drug product will be supplied in blister packs containing two (2) 90 mg, (equivalent to 100 mg rolapitant hydrochloride monohydrate) tablets provided by TerSera. Study drug supplies must be stored in a secure, limited-access location under the storage conditions specified on the drug supply label. Rolapitant tablets are stored at Controlled Room temperature, 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) (25).

### C. Additional Clinical Supplies

For additional supplies, the pharmacist will coordinate the dispatch of supplies to the site.

### D. Drug Accountability

It is the responsibility of the clinical investigator or trained designee to ensure that all study drug received at the site is inventoried and accounted for throughout the study by

the designated personnel and is recorded in the inventory log kept with the pharmacy study documentation. The drug accountability will be verified by a trained designee upon completion of the study. Study drug will be stored in a secured area with restricted access to the dosing preparers only.

The clinical investigator or trained designee must store all study drug pending reconciliation. The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Investigator Agreement or their qualified designees. The investigator, sub-investigators, or qualified designees also agree that the study drug(s) will be dispensed only to study subjects who have provided written informed consent and have met all entry criteria and in accordance with the instructions provided in the pharmacy manual.

After study drug reconciliation, the clinical site may destroy used/unused study drug product locally in accordance with all applicable institutional standard operating procedures, local and federal laws. Documentation of such destruction must be recorded and provided TerSera. If the clinical site does not have the appropriate procedures in place to handle final disposition of clinical supplies, the clinical site will be instructed to return the clinical supplies to TerSera.

### 3.2 Fosaprepitant
Fosaprepitant iv will be used from the commercial source.

### 3.3 Other Drugs
Doxorubicin, ifosfamide, vincristine, mesna, and hematopoietic growth factors are all commercially available drugs (see dose modification table in Section 5.3).

## 4.0 Patient Eligibility

### Inclusion Criteria
- Patients with sarcoma which is locally advanced, at high risk for relapse or metastatic for whom treatment with doxorubicin plus ifosfamide (AI) or AI and vincristine (VAI) is indicated.
- Must be 18 to 65 years of age.
- Patient must have an estimated life expectancy ≥ 4 months in the opinion of the investigators.
- Male and Females of child bearing potential must use acceptable methods of birth control which include oral contraceptives, spermicide with either a condom, diaphragm or cervical cap, us of a intrauterine device (IUD) or abstinence.
    - Female patients must have a negative pregnancy test at Screening
    - Female patients of childbearing potential must agree to use an acceptable method of birth control (excluding hormonal birth control methods) for 72

hours prior to admission and to continue its use during the study and for at least 30 days after the final dose
- Male patients must agree to use an acceptable form of birth control from study Day 1 through at least 30 days after the final dose

- Adequate hematologic (ANC > 1500/$mm^3$, platelet count > 100,000/$mm^3$), renal (serum creatinine < 1.5mg/dL), hepatic [serum bilirubin count < 1.5 x upper limit normal (ULN) and SGOT or SGPT < 2.5 x ULN, for subjects with known liver metastases < 5 x ULN] functions.
- Karnofsky Performance Status > 60%. (Appendix D)
- Signed informed consent form.
- Patients are required to read and understand English to comply with protocol requirements.

**Exclusion Criteria**

a. Any current treatment, medical history, or uncontrolled condition, other than malignancy, (e.g., alcoholism or signs of alcohol abuse, seizure disorder, medical or psychiatric condition) that, in the opinion of the investigator, would confound the results of the study or pose any unwarranted risk in administering study drug to the subject
b. Patient has a known hypersensitivity to the administration of any prescribed oral or intravenous study medication or metabolite, including but not limited to, a history of hypersensitivity to the drugs or their components, severe renal impairment, severe bone marrow suppression, or systemic infection
c. Patient is a woman with a positive urine or serum pregnancy test within 3 days prior to study drug administration, is breast-feeding, or is planning to conceive children within the projected duration of the study treatment
d. Patient has taken the anti-emetic agents within the last 48 hours prior to the start of treatment with study drug:
    - 5-$HT_3$ antagonists (ondansetron, granisetron, dolasetron, tropisetron, etc.). Palonosetron is not permitted within 7 days prior to administration of investigational product
    - Phenothiazines (prochlorperazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine, etc.)
    - Benzamides (metoclopramide, alizapride, etc.)
    - Domperidone
    - Cannabinoids
    - NK1 antagonist (aprepitant)
    - Benzodiazepines (lorazepam, alprazolam, etc)
    - herbal medications or preparations in doses designed to ameliorate nausea or emesis

e. Patient has received systemic corticosteroids or sedative antihistamines (dimenhydrinate, diphenhydramine, etc.) within 72 hours of Day 1 of the study except

as premedication for chemotherapy (e.g., taxanes). Subjects who are receiving inhaled steroids for respiratory conditions or topical steroids for skin disorders can be enrolled

f. Patient has symptomatic primary or metastatic CNS disease
g. Patient has ongoing vomiting, retching, dry heaves, or clinically significant nausea caused by any etiology, or has had such symptoms within 24 hours prior to the start of Day 1 of the study intervention, or has a history of anticipatory nausea and vomiting
h. Patient must not have been dosed with test drug or blinded study drug in another investigational study within 30 days or 5 half-lives of the biologic activity of the test drug, whichever is longer, before the time of first study dose
i. Patient who is participating in any investigational agent that is not FDA-approved.
j. Patient has uncontrolled angina, congestive heart failure (New York Heart Association > class II or known ejection fraction < 40%), uncontrolled cardiac arrhythmia or hypertension, or acute myocardial infarction within 3 months.
k. Prior surgery or radiotherapy (RT) within 2 weeks of study entry.
l. Psychological, social, familial, or geographical reasons that would prevent scheduled visits and follow-up.

## 5.0 Treatment Plan

### 5.1 Study Drug Treatment

This study will be conducted in 2 parts, part I and Part II, as follows:

**Part I:**

This part will be a single-arm phase II study of rolapitant administered as single-dose on Day 1. In this part, we will estimate the preliminary efficacy of rolapitant administered on day 1 by evaluating complete response (CR) in the single arm setting.

Up to 42 patients will be enrolled in part 1 (after the amendment 4) using the Simon's Minimax 2-stage design; 24 patients will be enrolled in the first stage. If ≥ 2 out of 24 patients experience CR, additional 18 patients will be enrolled. The trial will be stopped early if less than 8 patients have complete response in nausea/vomiting.

With conclusion of Part 1 of study, communication of Part 1 study results will be presented to TerSera. In addition, publication of Part 1 study results may be presented for poster abstract and/or scientific journal for publication.

The decision to move on to Part II of this study will not depend on the results of the patients who have been treated with dexamethasone at 8 mg on Days 2-5. Rather, if the first part of the trial for the patients who will be treated with dexamethasone at 12 mg on Days 2-5 was not stopped early due to lack of efficacy of rolapitant and TerSera consents to continuation of the trial, the trial will proceed to the second part of the trial.

**Treatment Plan:**
All patients will receive anti-emetics approximately 1- 2 hrs prior to chemotherapy infusion as follow: Dexamethasone IV daily for 5 days (12 mg on days 1-5, after the amendment 2), Ondansetron (5HT3 receptor antagonist) 16 mg IV daily for 5 days as standard of care, and Rolapitant, 180 mg will be administered PO on Day 1. For 5-days Ifosfamide regimen, the anti-emetics will be given for 6 days.

**Part II:** This part will be a randomized, 2-arm phase II study of rolapitant vs fosaprepitant. If the trial was not stopped early, then the trial will proceed to the second part.

Assuming 40% and 11% CR rates in Arm A, and Arm B respectively, approximately 78 evaluable subjects will be randomly assigned to receive Rolapitant or fosaprepitant (1:1) administered as a single dose. The fosaprepitant arm will be used as standard arm to prevent patient selection bias.

**Treatment Plan:**
Patients will be randomized into two treatment arms:
Arm A/ investigational arm: single dose of rolapitant n=39.
Arm B/ control arm: single dose of fosaprepitant, n=39.

**Arm A**/ investigational arm: all patients (n=39) will receive anti-emetics approximately 1-2 hrs prior to chemotherapy infusion as follow: Dexamethasone IV daily for 5 days (12 mg on days 1-5), Ondansetron (5HT3 receptor antagonist) 16 mg IV daily for 5 days as standard of care, and Rolapitant, 180 mg will be administered PO on Day 1.

**Arm B**/control arm: all patients (n=39) will receive anti-emetics approximately 1- 2 hrs prior to chemotherapy infusion as follow: Dexamethasone IV daily for 5 days (12 mg on day 1, and 8 mg on days 2-5), Ondansetron (5HT3 receptor antagonist) 16 mg IV daily for 5 days as standard of care, and Fosaprepitant 150 mg will be administered IV on Day 1.

If patients don't achieve complete response to Fosaprepitant in cycle 1 in the control arm, they can be given 2 doses of fosaprepitant on days 1 and 4 in cycle 2.

**Breakthrough nausea/vomiting and concomitant Medications**
Patients may take the following agents for breakthrough nausea as needed: Ondansetron, Lorazepam, Diphenhydramine, and Promethazine.

**5.2 Chemotherapy**
**AI Regimen:**
**Ifosfamide:** A total dose of 10 g/m$^2$ will be administered by IV bolus over 3 hours on days 1, 2, 3, 4 (2.5 g/m$^2$/day); or on days 1, 2, 3, 4, 5 (2 g/m$^2$/day).

**Doxorubicin:** 25 mg/m$^2$/day IV continuous infusion for 72 hours on days 1, 2, and 3, completing infusion on day 4 (total dose: 75 mg/m$^2$).

**Mesna:** For Ifosfamide over 4 days: Prior to ifosfamide (Day 1) - 500 mg/$m^2$ (20% of ifosfamide dose) given simultaneously with ifosfamide and then daily continuous infusion (Days 1-4 completing infusion on day 4) – 1,500 mg/$m^2$/day (60% of daily ifosfamide dose) for a total of 6 gm/$m^2$. For Ifosfamide over 5 days: Prior to ifosfamide (Day 1) - 400 mg/$m^2$ (20% of ifosfamide dose) given simultaneously with ifosfamide and then daily continuous infusion (Days 1-5 completing infusion on day 5) – 1,200 mg/$m^2$/day (60% of daily ifosfamide dose) for a total of 6 gm/$m^2$. The mesna infusion will complete 24 hours after the last dose of ifosfamide.

**Vincristine:** 2 mg IV by rapid infusion (Day 1) may be given to the patients with sarcomas of small cell histology.

The chemotherapy cycles will be repeated around every 3 weeks if ANC > 1,500/$mm^3$ and platelet count > 100,000/$mm^3$ and the patient has recovered from any acute toxicities of chemotherapy.

### 5.3 Supportive Care
Hematopoietic growth factors will be administered as per standard of care. All chemotherapy and growth factors will be used from commercial sources.

### 5.4 Dose Modifications
Every attempt will be made to deliver a minimum of 1 cycle of AI chemotherapy to each patient on the AI regimen. In the case of the specific adverse events related to chemotherapy, dose reductions of doxorubicin and/or ifosfamide may be carried out as per standard practice.

### 5.5 Duration of Therapy:
Cycle 1 will be considered as the study cycle.

Patients can receive up to a total of 6 cycles of chemotherapy in the absence of progressive disease and intolerable toxicity related to the study drug. Patients can receive Rolapitant or fosaprepitant, whichever arm they were assigned originally, in subsequent cycles (cycles 2-6). The patients will continue to report adverse events including nausea/vomiting in daily symptom record diary during cycles 2-6. In addition, the patients need to fill out the FLIE questionnaire (Appendix E) in cycle 1 (e.g. days 5 and 10) to monitor the improvement in nausea/vomiting.

Therapy will be continued for at least 1 cycle unless there is a rapid progression of disease, and for additional 5 cycles, if there is stable or responding disease and if unacceptable toxicity is not observed (maximum total 6 cycles).

## 6.0 Pretreatment Evaluation

- Standard History and Physical examination including weight and height.
- Karnofsky performance status ≥ 60% (PS appendix D)
- Laboratory studies will include a CBC with differential, and platelet count, electrolytes and serum chemistries.
- Serum beta hCG or urinary pregnancy test (when indicated).
- All screening labs/pretreatment evaluations can be done within 30 days before registration.

## 7.0 Evaluation During Study

- Interim History and Physical examination including weight will be done before each cycle of chemotherapy.
- Patients will report on daily symptom record diary the adverse events, the date of all emesis episodes, intensity of nausea, and rescue medications before and during study on days 1-10 of the first cycle. Also, patients will report the functional evaluations of nausea and emesis according to Functional Living Index-Emesis (FLIE) scale in cycle 1 ( e.g. days 1, 5 and 10) (26). In addition, the patients will continue to report on daily symptom record diary the adverse events while on study.
- Serum electrolytes and chemistries will be performed prior to every cycle and as frequently as needed during the cycle to monitor the toxicity
- Management of hypersensitivity to the study drug: Patients with allergic reactions can be symptomatically managed. All patients with grade 4 hypersensitivity reactions (anaphylaxis) will be removed from the study.

## 8.0 End of Study/Early Withdrawal

At their last clinic visit on the study, standard History and Physical examination including weight will be documented. Laboratory studies will include a CBC with differential, and platelet count.

## 9.0 Criteria for Response

### 9.1 Response

All patients who receive one dose of study drugs (Rolapitant and fosaprepitant) under this protocol will be evaluable for response and toxicity.

**9.2** The severity of nausea will be reported in patients diary using 4-point scale (Likert scale), as 0 (none), 1 (mild), 2 (moderate), and 3 (severe) during cycle-1 of chemotherapy.

**9.3** Response will be defined as 0-24 hours, 24-120 hours, 120-240 hours, and overall period.

**Complete response (CR):** No emetic episodes and no rescue medications.
**Complete control (CC):** CR and no more than mild nausea.

**9.4** Toxicity: Toxicities will be graded using the Common Terminology Criteria for Adverse Events v4.03 – CTCAE (see Appendix C). Uncomplicated, severe, or life threatening neutropenia and thrombocytopenia are expected toxicities of the study chemotherapy regimen and as such will not be collected as adverse events in this study since the data is already captured through the PDMS/CORE.

## 10.0 Criteria for Discontinuation from Treatment

Patients may be discontinued from study treatment at any time. Specific reasons for discontinuing treatment include the following:

- Serious or life-threatening adverse event
- Risk to patients as judged by the Investigator and/or Sponsor
- Severe noncompliance with protocol as judged by the Investigator and/or Sponsor
- Request of the patient
- Patient becomes pregnant
- Progressive disease
- Investigator becomes aware of conditions or events that suggest a possible hazard to patients if the clinical study continues

### 10.1 Discontinuation from Study

Patients who discontinue from treatment will continue to receive follow-up assessments as part of the study unless they are discontinued from study by one of the following events:

- Withdrawal of consent
- Loss to follow-up
- Death from any cause
- Termination of the study

## 11.0 Statistical Consideration and Sample Size

### Statistical Considerations and Analysis

This is a phase II trial to study the treatment efficacy of rolapitant on nausea/vomiting in patients with sarcoma receiving multi-day chemotherapy with doxorubicin and ifosfamide regimen (AI). This trial will be carried out in two parts. The primary goal of the first part of the trial is to estimate the preliminary efficacy of rolapitant administered as single-dose on Day 1 by evaluating complete response (CR) rate in a single-arm setting. The primary objective of the second part of the trial is to establish the efficacy of rolapitant

administered as single-dose on Day 1 by evaluating CR rate in comparison with the efficacy of fosaprepitant administered as single-dose on Day 1.

**Design and sample size/power**

**Part I: A single-arm phase II study of rolapitant administered as single-dose on Day 1**

We will assess the efficacy of rolapitant on nausea/vomiting by evaluating CR rate using the Simon's Minimax 2-stage design (27). A patient will be considered as to have a CR if s/he does not experience chemotherapy related emesis and do not need rescue medication during cycle-1 following initiation chemotherapy. The primary endpoint is CR rate in cycle 1 (days 1-10). In our previous study, we observed 2 (11%) CRs among 18 patients who were treated with the standard of care. Based on the data of the 19 patients currently enrolled into this study, 6 out of 19 patients (32%) experienced CR. Therefore, a CR rate of 11% or less is considered as clinically insignificant, while a CR rate of 32% or higher is considered as clinically significant. When the probability of accepting an ineffective regimen (CR rate ≤ 11%) is 0.05 and the probability of rejecting an effective regimen (CR rate ≥ 32%) is 0.05, the Simon Minimax 2-stage design requires 24 patients in the first stage. The drug will be rejected if no more than 2 responses are seen in the first stage. Otherwise, another 18 patients will be accrued. At the end of the trial, the drug will be rejected if no more than 8 responses are observed in a total of 42 evaluable patients (maximum accrual 47 patients; 42 evaluable, potential 10% drop out rate). The trial will be stopped early 50% of the time, and the mean sample size of the trial will be 33 if the true response rate is 11%. Accrual will be halted after the 24th patient is enrolled until 3 or more responses are seen in the first stage.

Since there is no interaction between rolapitant and CYP3A4, the dose of dexamethasone will not be reduced from 12 mg to 8 mg and will be kept constant at 12 mg on Days 2-5 for Part 1 (Rolapitant), and Arm A (Rolapitant) of the Part 2 as stated in "Treatment Plan" section. After 9 patients were accrued to the first phase of Part I of the study with a dose of dexamethasone at 8 mg on Days 2-5, the protocol was amended to keep dexamethasone dose constant at 12 mg on Days 2-5. Up to date, 19 patients have been enrolled and treated with dexamethasone at 12 mg on Days 2-5 as a new cohort for the first stage of the Simon's Minimax 2-stage design, additional 5 patients will be accrued and treated in the first phase of Part I of the study as soon as this amendment is approved by IRB. The same rules of the design aforementioned will be applied.

**Part II: A randomized, 2-arm phase II study of rolapitant vs fosaprepitant**

The decision to move on to Part II of this study will not depend on the results of the patients who have been treated with dexamethasone at 8 mg on Days 2-5. Rather, if the first part of the trial for the patients who will be treated with dexamethasone at 12 mg on Days 2-5 was not stopped early due to lack of efficacy of rolapitant, the trial will proceed to the second part of the trial. This will be a randomized, 2-arm trial of rolapitant administered as single-dose on Day 1 in patients with sarcoma receiving multi-day

chemotherapy with Doxorubicin and Ifosfamide regimen (AI). Arm A patients will receive a single dose of rolapitant on Day 1; Arm B patients will receive a single dose of fosaprepitant on Day 1. The primary objective is to evaluate the effect of rolapitant on nausea/vomiting as compared to the effect of a single dose of fosaprepitant in cycle 1 (days 1-10). Again, a patient will be considered as to have a complete response (CR) if s/he does not experience emesis and do not need rescue medication during cycle-1 following initiation chemotherapy. The primary endpoint is CR rate in cycle 1 (days 1-10). The sample size for this part of the trial will depend on the CR rate observed in the first part of the trial. Table 1 shows sample sizes required for three presumably observed CR rates in the first part of the trial assuming that the CR rate in Arm B is 11%. For example, a total of 78 patients, 39 in each arm, will provide the study 80% power to detect the differences of CR rates between the two arms using a Fisher exact test with a 0.05 two-sided significance level when the respective CR rates are 40% and 11% in Arm A, and B (15, 16). All patients that complete cycle-1 (days 1-10) of chemotherapy will be considered evaluable for the study. Patients that can't complete cycle-1 of chemotherapy due to disease progression, treatment change, withdrawal of consent, or other reasons will be replaced with new patients (maximum accrual 86 patients; 78 evaluable, potential 10% drop out rate) nQuery 7.0 was used for the sample size or power calculation.

Table 1. Sample size needed per arm in testing difference in complete response rate during cycle-1 between Arm A and B, Fisher's exact test with two-sided significance level of 0.05 and 80% power assuming the CR rate of Arm B is 11%

| CR rate in Arm A | 30% | 40% | 45% | 50% |
|---|---|---|---|---|
| Sample size | 78 | 39 | 31 | 24 |

**Analysis Plans**

Patients' demographic and clinical characteristics at baseline will be summarized using descriptive statistics such as mean, standard deviation, median, interquartile range (IQR), frequency where appropriate. We will apply Student t-test/Wilcoxon test and Kruskal-Wallis test/ANOVA to compare continuous variables between different patient group, and the chi-square test or the Fisher's exact test to assess the association between two categorical variables (28).

For the analysis of the primary endpoint of the first part of the trial, we will provide point estimate along with 95% exact confidence interval (CI) of CR rate.

For the analysis of the primary endpoint of the second part of the trial, Fisher exact test will be used to test the difference of CR rates between the two arms. CR rates along with their 95% confidence intervals (CIs) will be estimated by study arm. We will use logistic regression model (28) to assess the effect of patient specific covariates, such as treatment group, gender, etc. on the complete response. The secondary endpoints are the response rates in each of the time periods (0-24 hours, 24 hrs-120 hrs, and 120-240 hours). Logistic regression models using generalized estimating equations (GEE) will be

used to fit the response data to take the intra-patient correlation into account and to compare the differences of the response rates between the two treatment arms and to evaluate the effects of the patient specific covariates(29).

Toxicity data will be summarized by frequency tables for all patients and by treatment arm. For the efficacy endpoint, intent-to-treat analysis will be applied to the eligible patients. For the toxicity endpoint, per-treated analysis will be used to include any patient who received the treatment regardless of the eligibility nor the duration or dose of the treatment received.

If there are missing data, the reasons for missing data will be recorded, and missing-data mechanism will be checked. For data missing at random (MAR), multiple imputation techniques implemented in SAS PROC MI procedure to handle missing data will be used. For data missing not at random (MNAR), methods that add an explicit model for the missing mechanism to the data model will be applied.

The data from the patients who were treated with dexamethasone at 8 mg on Days 2-5 (prior to amendment 2) will be analyzed separately and included in relevant reports.

**Randomization**
Randomization will be carried out via CORe.

## 12.0 Data and Protocol Management

Data will be collected and entered in PDMS/CORE by the research staff assigned to the study.

### 12.1 Good Clinical Practice
The conduct of the study will conform to the recommendations for clinical studies in human subjects as per the guidelines on “Good Clinical Practice”, [21 CFR Part 312 and ICH guidelines].

## 13.0 Serious Adverse Events and reporting requirement

### 13.1 Reporting Product Quality Complaints for Rolapitant
Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the sponsor-investigator or qualified designee to TerSera Call Center (tersera@medicalinfodept.com) within 1 working day of first becoming aware of the possible defect. This report to TerSera may be made by telephone to the designated TerSera representative (1-844-334-4035) or by fax to the call center (1-913-451-6409). The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect.

If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

**13.2 Adverse Events**

An adverse event (AE) is any new, undesirable medical occurrence or change (worsening) of an existing condition in a subject that occurs during or after treatment, whether or not considered to be product related. Therefore, adverse events are treatment-emergent signs or symptoms. In this study, the following adverse effects are expected and will not be reported. They will be summarized in the updated and final analysis. Myelosuppression and its associated complications are part of the treatment of sarcoma with high dose AI. Therefore, low blood counts and related complications such as infections, bleeding and hospitalizations due to myelosuppression will not be reported as severe adverse drug reactions related to Rolapitant.

AEs will be collected from the time of informed consent to 30 days after last study drug administration. AEs that occur before the first study drug administration, concomitant illnesses, which existed before study entry, but did not worsen during the treatment period and any pre-existing conditions are known as “pre-treatment AEs” and by definition are “unrelated” to study drug. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, electrocardiograms [ECG], reported by patient), must be documented.

Each AE will be assessed by the Investigator with regard to the intensity.
Intensity should be assessed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v.4.03, Appendix C). Attribution of adverse events (AE) to study treatment will be recorded as follows:

- Related: The AE is clearly related to the study treatment.
- Possible Related: The AE may be related to the study treatment.
- Unlikely Related: The AE is doubtfully related to the study treatment.
- Unrelated: The AE is clearly NOT related to the study treatment.

**Follow-up of Adverse Events**

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

**13.3 Serious Adverse Events**

A serious adverse event is defined by regulatory agencies as one that suggests a significant hazard or side effect that occurs (at any dose) and results if the event:

- is fatal

- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy, disease-related procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events)
- is a persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias. If the adverse event is sufficiently severe in the investigator's judgment, the subject should be removed from treatment and a termination assessment performed. The subject should be given appropriate care under medical supervision until symptoms cease.

**The relationship to study drug therapy should be assessed using the following definitions:**

**Deaths:**
All deaths occurring on study must be reported. These include deaths within 30 days of the last investigational product dose and deaths up to the last formal follow-up observational period. In addition, any death, which occurs after the protocol has ended, but is felt to be related to the study drug, must be reported to the FDA.

**All serious adverse events will be reported to the University of Texas M.D. Anderson Cancer Center IRB within five working days of knowledge of the event.**

**13.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)**
For any AE that is serious, associated with the use of the study treatment, and unexpected (defined as any term not listed in the expectedness section of the current Prescribing Information) additional reporting requirements are described below. These types of reports are referred to as (SUSARs).

- If the SUSAR is fatal or life-threatening, associated with the use of the study treatment, and unexpected, Regulatory Authorities and Independent Ethics Committees (IECs) will be notified within 7 calendar days after the Investigator learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the study treatment, and unexpected, Regulatory Authorities and IECs will be notified within 15 calendar days after the Investigator learns of the event.

The Institution will also provide annual safety updates to the Regulatory Authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

**13.5 Pregnancy**

Pregnancies occurring in a female patient or a female partner of a male patient and pregnancy outcomes must be reported within 24 hours to the Institution contact provided above. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Spontaneous abortions should always be reported as SAEs.

The Investigator should follow-up with the study patient or the female partner of the study patient until delivery or termination of pregnancy, even if the patient was withdrawn from the clinical study or the clinical study was completed. The Company will be informed of all pregnancy outcomes.

**13.6 Sponsor SAE and Pregnancy Reporting to TerSera**

Institution will forward all treatment emergent SAE reports (MedWatch or CIOMS I form) regardless of causality, to TerSera within 24 hours of completion of the final report. The institution will forward both final initial and follow-up versions of each SAE report. The Institution will also provide reports for all pregnancies in the same manner.

**TerSera Contact Details**

- Email: tersera@medicalinfodept.com
- Fax: 1.913.451.6409

Investigators must report to the Institution any SAE occurring after the signing of informed consent until 30 days following last study drug treatment and within 24 hours of becoming aware of the event.

**14.0 Monitoring Plan:** All protocol participants will be registered in CORE. The principal investigator will be responsible for submitting SAE's to the IRB. SAE's will be submitted to OPR and entered into CORE.

## References

1. Griffin AM, Butow PN, Coates AS, et al. On the receiving end. V: Patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol. 1996; 7:189-195.
2. Osoba D, Zee B, Warr D, Kaizer L, et al. Quality of Life Studies in Chemotherapy-Induced Emesis. *Oncology*. 1996; 53:92-95.
3. Hasketh PJ. Chemotherapy-induced nausea and Vomiting. NEJM 358; 23: 2482-2494
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: antiemesis v.1.2004. American Cancer Society. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.aspAccessed october 25, 2011.
5. Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Annals of Oncology, 2010,21:(Suppl 5) 232-243.
6. Kris MG, Tonato M, Bria E, et al. Consensus recommendations for the prevention of vomiting and nausea following high-emetic-risk chemotherapy. Support Care Cancer 2011, 19:Suppl 1:S25-32 Epub 2010 Aug. 28.
7. Marty M, Pouillart P, Scholl S, et al. Comparison of the 5-hydroxytryptamine3 (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med.* 1990; 322:816-821.
8. De Mulder PH, Seynaeve C, Vermorken JB, et al. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. A multicenter, randomized, double-blind, crossover study. *Ann Intern Med*. 1990; 113:834-840.
9. Cohen L, de Moor C, Eisenberg S, et al. Delayed chemotherapy-induced nausea and vomiting (CINV) remains a problem and significantly interferes with daily functioning (DF) in pts receiving emetogenic chemotherapy (CT) in the United States [abstract]. *Proc Am Soc Clin Oncol* 22:739, 2003. Abstract 2972.
10. Roila F, Fatigoni S. New antiemetic drugs. Annals of Oncology 2006; 17 (Suppl 2): ii96-ii100.
11. Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. Ann Pharmacother. 2005 Jan;39(1):77-85. Epub 2004 Nov 23.
12. Hesketh PJ, Grunberg SM, Gralla RAJ, et al. The oral neuokinin-1 antagonist aprepitant for the prevention of chemotherapy- induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin –the Aprepitant protocol 052 Study Group. J Clin Oncol. 2003 Nov 15;21(22):4112-9. Epub 2003 Oct 14
13. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double –blind, placebo-controlled trial in Latin America. Cancer 2003;97(12):3090-8.

14. Warr DG, Hesketh PJ, Gralla RJ, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. JCO 2005; 23(12): 2822-30.
15. Vadhan-Raj S, Zhou X, Araujo DM, et al. Effects of fosaprepitant (Fosa) administered as single dose versus two doses, on nausea/vomiting (N/V) in patients receiving multiday chemotherapy (CT) with a highly emetogenic regimen of doxorubicin and ifosafamide (AI): Randomized cross-over study. J Clin Oncol 32:5s, 2014 (suppl; abstr 9616)
16. Vadhan-Raj S, Zhou X, Spasojevic I et al. Randomized, cross-over study of fosaprepitant (single dose vs two doses) for nausea and vomiting in sarcoma patients receiving multiday chemotherapy. Supportive Care Cancer (2015) 23 (Suppl): S1-S388
17. Duff y RA, Morgan C, Naylor R, et al. Rolapitant (SCH 619734): a potent, selective and orally active neurokinin NK-1 receptor antagonist with centrally-mediated antiemetic effects in ferrets. Pharmacol Biochem Behav 2012; 102: 95–100.
18. Poma A, Christensen J, Davis J, et al. Phase 1 positron emission tomography (PET) study of the receptor occupancy of rolapitant, a novel NK-1 receptor antagonist. J Clin Oncol 2014; 32 (suppl): abstr e20690.
19. Olver I. Role of rolapitant in chemotherapy-induced emesis. Lancet Oncol. 2015 Aug 10. pii: S1470-2045(15)00096-0.
20. Romero D. Chemotherapy: Rolapitant-a new and safer antiemetic agent. Nat Rev Clin Oncol. 2015 Aug 25. doi: 10.1038/nrclinonc.2015.144.
21. Rapoport B, Chua D, Poma A, et al. Study of rolapitant, a novel, long-acting, NK-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting (CINV) due to highly emetogenic chemotherapy (HEC). Support Care Cancer 2015, published online May 5. DOI:10.1007/s00520-015-2738-1.
22. Rapoport BL, Chasen MR, Gridelli C, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. Lancet Oncol. 2015 Aug 10. pii: S1470-2045(15)00035-2.
23. Gan TJ, Gu J, Singla N, et al. Rolapitant Investigation Group. Rolapitant for the prevention of postoperative nausea and vomiting: a prospective, double-blinded, placebo-controlled randomized trial. Anesth Analg. 2011 Apr;112(4):804-12
24. Schwartzberg LS, Modiano MR, Rapoport BL, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. Lancet Oncol. 2015 Aug 10. pii: S1470-2045(15)00034-0.
25. http://varubirx.com/downloads/VARUBI_(rolapitant)_Full_Prescribing_Information_September_2015.pdf
26. Martin AR, Pearson JD, Cai B, et al. Assessing the impact of chemotherapy-induced nausea and vomiting on patients' daily lives: a modified version of the

Functional Living Index-Emesis (FLIE) with 5-day recall. Support Care Cancer. 2003 Aug;11(8):522-7.
27. Simon R. Optimal Two-Stage Designs For Phase II Clinical Trials. Controlled Clinical Trials 10:1-10, 1989
28. Woolson, RF and Calrke, WR. Statistical Methods for the Analysis of Biomedical Data. 2nd Edition, John Wiley & Sons, New York, 2000.
29. Hosmer DW, Lemeshow S. Applied logistic regression. 2nd Edition, Wiley, New York, 2000.