Official Protocol Title:	A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-0517/Fosaprepitant and Ondansetron Versus Ondansetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Subjects Receiving Emetogenic Chemotherapy
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TITLE:

A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-0517/Fosaprepitant and Ondansetron Versus Ondansetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Subjects Receiving Emetogenic Chemotherapy

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1.0 TRIAL SUMMARY

Abbreviated Title	Single Dose of MK-0517 for Prevention of CINV in Pediatric Subjects
Trial Phase	III
Clinical Indication	Prevention of nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic chemotherapy in pediatric subjects
Trial Type	Interventional
Type of control	Placebo
Route of administration	Intravenous (IV)
Trial Blinding	Double-blind
Treatment Groups	Group 1: fosaprepitant + ondansetron Group 2: placebo for fosaprepitant + ondansetron
Number of trial subjects	Approximately 180 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 23 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for approximately 43 days from the time the subject/parent/guardian signs the Informed Consent/Assent Form (ICF) through the final contact. After a screening phase of up to 28 days, each subject will be receiving assigned treatment for approximately 1 day. After the end of treatment each subject will be followed for 14 days. **Note:** Subjects may have the option to participate in up to 5 additional open-label cycles. Each optional cycle will be approximately 15 days.
Randomization Ratio	1:1

A list of abbreviations and definitions used in this document can be found in Section 12.7 - Abbreviations and Definitions.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind trial to evaluate the efficacy and safety of fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV). Subjects must be scheduled to receive chemotherapeutic agent(s) associated with moderate or high risk of emetogenicity, or chemotherapy agent(s) not previously tolerated due to vomiting. This study is to be conducted in conformance with Good Clinical Practices.

This study will endeavor to enroll an approximately even distribution of subjects into the following four age groups, but final enrollment in age groups may differ:

- Birth to <2 years,

- 2 to <6 years,
- 6 to <12 years,
- 12 to 17 years.

Subjects <12 years of age will NOT be permitted to participate in the current study until Pharmacokinetic/Pharmacodynamic (PK/PD) and safety data from an ongoing PK/PD and safety study (MK-0517 Protocol 029) can be evaluated to confirm the planned dose adjustments for subjects <12 years of age. Enrollment of subjects <12 years of age will begin once the study sites are notified of the final dosing instructions via a written letter from the SPONSOR. The age categories may be adjusted if PK/PD data from the ongoing Protocol 029 do not support opening enrollment for one or more age group(s).

This study will evaluate a single dose of fosaprepitant dimeglumine (EMEND® for Injection), hereafter referred to as 'fosaprepitant', in combination with the 5-hydroxytryptamine 3 ($5\text{-}HT_3$) antagonist ondansetron. Subjects will be randomized into 1 of 2 treatment regimens with a 1:1 ratio and will receive either a single IV dose of fosaprepitant in combination with IV ondansetron beginning on Day 1 of emetogenic chemotherapy or IV ondansetron concomitantly with a matching placebo for fosaprepitant. IV dexamethasone may be administered as part of the antiemetic regimen at the discretion of the investigator. Chemotherapy naïve and non-naïve subjects are permitted to participate in the study. Randomization will be stratified by age, planned use of High Risk emetogenic chemotherapy agent in Cycle 1 and planned use of dexamethasone as an antiemetic in Cycle 1.

The main objectives of this study will be assessed during a single chemotherapy cycle (Cycle 1), where study medication will be administered in a double-blind manner. Upon completion of Cycle 1, eligible subjects may be invited to participate in an open-label fosaprepitant treatment period for up to 5 more cycles of chemotherapy. Participation in open-label Cycles 2 to 6 is optional. All subjects will be allowed a maximum of 6 months from the end of Cycle 1 to complete Cycles 2 to 6.

In Cycle 1, subjects may be screened up to 28 days prior to randomization. Eligible subjects will then enter the double-blind treatment period and will be required to complete a Patient Diary for the 120 hours following the start of emetogenic chemotherapy administration. Subjects will be followed for 14 days after treatment with fosaprepitant or placebo to fosaprepitant. Subjects will have 4 clinic visits and phone/direct contact will be made on Days 2-5 of Cycle 1.

Subjects will be re-evaluated before entering optional Cycles 2 to 6 to determine if entry criteria have been met. Subjects will be followed for 14 days after his/her treatment with fosaprepitant in the last study cycle. There are 2 clinic visits during each optional cycle.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted below in Figure 1.

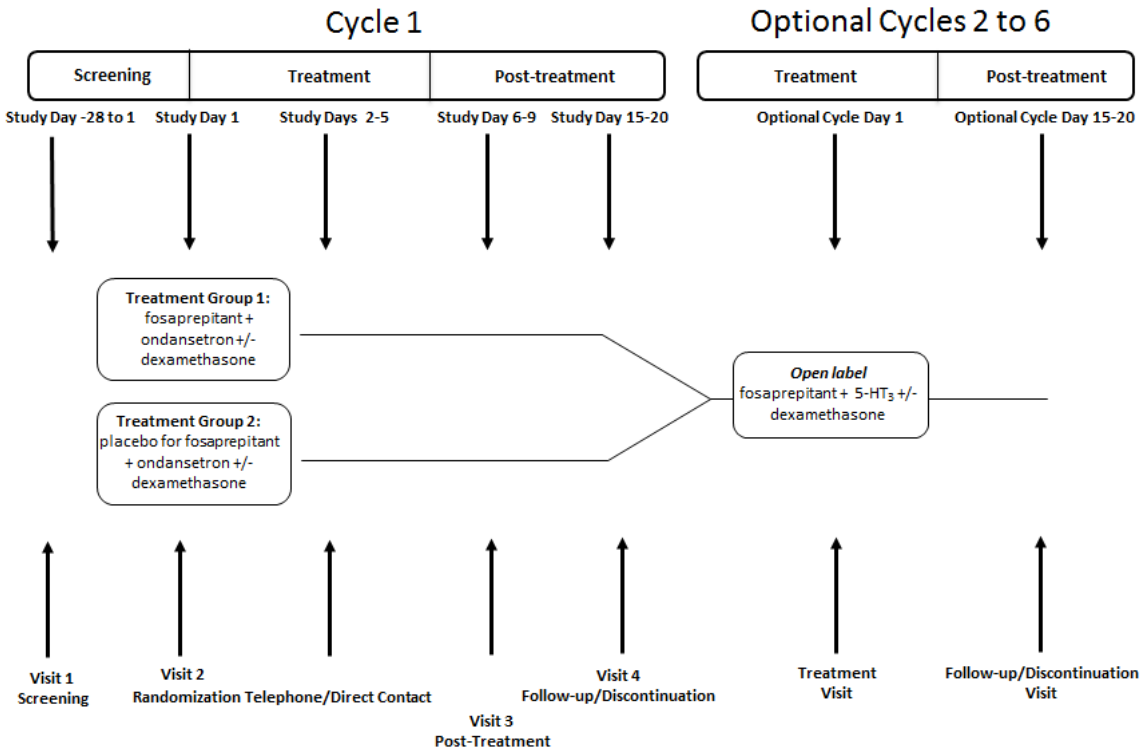

Figure 1 – Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To compare the single IV dose of fosaprepitant (in combination with ondansetron) to the ondansetron alone regimen with respect to the efficacy endpoint of Complete Response in the delayed phase (>24 to 120 hours) following the initiation of emetogenic chemotherapy in Cycle 1.

   Hypothesis: The single IV dose of fosaprepitant in combination with ondansetron with or without dexamethasone (hereafter referred to as the fosaprepitant regimen) provides superior control of CINV compared to ondansetron alone with or without dexamethasone (hereafter referred to as the control regimen) as measured by the

proportion of subjects with Complete Response (no vomiting, no retching, and no use of rescue medication) in the delayed phase (>24 to 120 hours) following the initiation of emetogenic chemotherapy in Cycle 1.

2) **Objective**: To assess the safety and tolerability of the fosaprepitant regimen in subjects birth to 17 years of age who are receiving emetogenic chemotherapy.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To compare the fosaprepitant regimen to the control regimen with respect to the efficacy endpoint of Complete Response in the acute phase (0 to 24 hours) following the initiation of emetogenic chemotherapy in Cycle 1.

   Hypothesis: The fosaprepitant regimen is superior to the control regimen as measured by the proportion of subjects with Complete Response in the acute phase (0 to 24 hours) following the initiation of emetogenic chemotherapy in Cycle 1.

2) **Objective**: To compare the fosaprepitant regimen to the control regimen with respect to the efficacy endpoint of Complete Response in the overall phase (0 to 120 hours) following the initiation of emetogenic chemotherapy in Cycle 1.

   Hypothesis: The fosaprepitant regimen is superior to the control regimen as measured by the proportion of subjects with Complete Response in the overall phase (0 to 120 hours) following the initiation of emetogenic chemotherapy in Cycle 1.

3) **Objective**: To compare the fosaprepitant regimen to the control regimen with respect to the efficacy endpoint of No Vomiting, regardless of rescue medication use, in the overall phase (0 to 120 hours) following the initiation of emetogenic chemotherapy in Cycle 1.

   Hypothesis: The fosaprepitant regimen is superior to the control regimen as measured by the proportion of subjects with No Vomiting, regardless of rescue medication use, in the overall phase (0 to 120 hours) following the initiation of emetogenic chemotherapy in Cycle 1.

3.3 Exploratory Objectives

1) To compare, in the 120 hours following initiation of emetogenic chemotherapy (overall phase) in Cycle 1, the fosaprepitant regimen to the control regimen with respect to:

   - The number of emetic episodes;
   - The number of subjects with no use of rescue medication;
   - The time to first rescue medication;

- The time to first vomiting.

2) To explore the efficacy of the fosaprepitant regimen versus the control regimen using alternatively defined acute (the period from the initiation of the first dose of emetogenic chemotherapy until 24 hours after initiation of the last dose of emetogenic chemotherapy) and delayed (end of the acute phase to 120 hours after the first dose of emetogenic chemotherapy) phases.

3) To compare aprepitant plasma concentrations profiles and pharmacokinetic parameters (e.g., $AUC_{0-\infty}$, AUC_{0-24}, C_{max}, T_{max}, $t_{1/2}$, CL/F, C_{24hr}, and C_{48hr}), in pediatric subjects from birth to 17 years old enrolled in Optional Cycle 2 to historical pharmacokinetic parameters obtained in adults.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) and approved labeling for detailed background information on fosaprepitant dimeglumine /MK-0517.

4.1.1 Pharmaceutical and Therapeutic Background

Substance P belongs to a family of neuropeptides known as tachykinins and is the preferred agonist for NK_1 receptors. In experimental models, NK_1-receptor antagonists have demonstrated potent, and usually long-lasting, anti-emetic activity against a broad spectrum of central and peripheral emetogens, whereas 5-HT_3 receptor antagonists show a more limited spectrum of activity with efficacy mostly against peripheral emetogens [1-3].

Brain penetrant NK_1-receptor antagonists, such as aprepitant, have been shown in multiple studies to be clinically effective in preventing nausea and vomiting associated with emetogenic chemotherapy [4-6]. Oral aprepitant (EMEND®) is a selective high-affinity antagonist of human substance P/NK_1 receptors that, when used in combination with 5-HT_3 receptor antagonists and corticosteroids, is highly effective in the prevention of acute and delayed nausea and vomiting due to highly and moderately emetogenic chemotherapy [4-7]. The use of aprepitant in adults has been approved for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC (March, 2003) and MEC (October, 2005). Due to the consistent demonstration of clinical benefit, a regimen of aprepitant administered as 125 mg on Day 1 followed by 80 mg on Days 2 and 3 is considered standard of care in adults for the prevention of nausea and vomiting associated with HEC and MEC [8-10]. Refer to the EMEND® Capsules prescribing information for more details. Aprepitant is not yet approved for use in children.

Fosaprepitant is a phosphoryl prodrug that is systemically converted to aprepitant within 30 minutes of intravenous administration. Thus, the pharmacological effect of fosaprepitant is attributed to aprepitant. A single IV dose of fosaprepitant 150 mg used concomitantly with a 5-HT_3 antagonist and a corticosteroid was demonstrated to be non- inferior to the 3-day oral aprepitant regimen in subjects receiving cisplatin-based HEC [11]. Based on these data,

fosaprepitant 150 mg has been approved in many countries as an alternative to the 3-day oral aprepitant regimen for the prevention of both HEC and MEC-associated CINV in adults; however, in some countries it has been approved for use only in HEC. Refer to the EMEND® for Injection prescribing information for more details. Fosaprepitant is not yet approved for use in children.

The aprepitant and fosaprepitant Investigator's Brochures (IBs) contain information about the physical, chemical, pharmaceutical, and formulation properties; preclinical and first in humans studies, as well as clinical studies conducted with these compounds.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

For children undergoing chemotherapy, the current Multinational Association of Supportive Care in Cancer (MASCC), European Society for Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO) guidelines recommend the use of 5-HT_3 antagonists, such as ondansetron, and corticosteroids to alleviate nausea and vomiting associated with emetogenic chemotherapy [8; 10]. However, despite the widespread use of these agents, nausea and vomiting continue to occur and remain a major source of distress for children undergoing emetogenic chemotherapy [12-14]. Thus, there is an ongoing need to evaluate the role of new anti-emetic agents such as fosaprepitant for pediatric CINV.

This study will evaluate the efficacy and safety of a single dose of fosaprepitant when administered concomitantly with ondansetron, with or without dexamethasone, in subjects birth to 17 years of age receiving emetogenic chemotherapy for a documented malignancy. The fosaprepitant dose included in this study is within exposures previously shown to be safe and well-tolerated in adult and adolescent subjects.

4.2.2 Rationale for Dose Selection/Regimen/Emetogenic Classification of Chemotherapeutic Agents

4.2.2.1 Rationale for Dose Selection

The approved regimen for fosaprepitant in adults for the prevention of CINV is a single IV dose of 150 mg. To support dosing in pediatric subjects, pharmacokinetic (PK) data are available from (1) an ongoing PK/PD (pharmacodynamic) pediatric study evaluating multiple dose levels of fosaprepitant (MK-0517 Protocol 029) and (2) a recently completed PK/PD pediatric study (MK-0869 Protocol 134) that included a cohort in which a single dose level of intravenous fosaprepitant was administered. Data from these studies and the aprepitant pediatric development program suggest that in adolescents ages 12 to 17 years, the adult dose (150 mg) is likely to achieve similar aprepitant PK exposures as observed in adults, and combined with exploratory efficacy data, this dose is appropriate for further evaluation in this study. In addition, no unexpected or concerning safety signals have emerged. Therefore, in the current study, the 150-mg single IV dose of fosaprepitant approved for adults was chosen as the dose for adolescent subjects.

Dosing for fosaprepitant in children < 12 years of age has also been evaluated in Protocols 134 and 029. Analyses of aprepitant PK following a single dose of fosaprepitant (doses up to 3 mg/kg) demonstrated lower aprepitant plasma exposures ($AUC_{0-\infty}$ and C_{min}) in children < 12 years of age as compared to adolescents and adults. These lower-than-expected PK exposures were particularly evident at extended time points (e.g., C_{48hr}, C_{72hr}). Although the exact mechanism for lower aprepitant plasma levels with decreasing age is not known, the data are consistent with previous studies that demonstrated increased hepatic clearance in younger children compared to adolescents and adults [15].

Further, exploratory data in children < 12 years of age suggest minimal if any incremental efficacy in the delayed phase following single fosaprepitant doses of 3 mg/kg given concomitantly with a 5-HT_3 antagonist, compared to a standard regimen of a 5-HT_3 antagonist alone (Protocol 134). Combined with the PK data described above, these data suggest that a single fosaprepitant dose greater than 3 mg/kg will be needed to obtain clinically meaningful efficacy for CINV, particularly in the delayed phase.

Based on additional modeling and simulation data, the Sponsor estimates that a fosaprepitant dose ~5.0 mg/kg (up to the maximum adult dose of 150 mg) will be needed to achieve aprepitant PK exposures and efficacy similar to that of adults. This fosaprepitant dose is predicted to result in aprepitant C_{max} levels of ~5000 ng/mL (for comparison, the aprepitant C_{max} value following 150 mg IV fosaprepitant in adults was ~4200 ng/mL). In early studies of healthy, young adults, aprepitant C_{max} levels up to ~9000 ng/mL were well-tolerated and therefore provide an adequate safety margin for the proposed 5.0 mg/kg dose.

Given these considerations, Protocol 029 was amended to allow confirmation of the expected PK and safety/tolerability in cohorts of children ages 0 to <2 years , 2 to < 6 years, and 6 to <12 years, prior to further evaluation in the current study (Protocol 044). In subjects 6 months to < 12 years of age the 5.0 mg/kg dose will be evaluated. Assuming there are no unexpected findings with respect to either PK or safety/tolerability, the current study will be opened for enrollment within each cohort as data become available. However, this dose may be adjusted based on PK, efficacy and/or safety/tolerability data from Protocol 029, and/or based on input from regulatory health authorities.

Neither aprepitant nor fosaprepitant have been evaluated in subjects younger than 6 months of age. In Protocol 029, pediatric subjects younger than 6 months of age will be enrolled and administered doses with a target PK profile similar to 150 mg fosaprepitant in adults as detailed above. The proposed doses for subjects younger than 4 months of age in Protocol 029 are further modified to account for expected reduced clearance due to immature expression of cytochrome P450 isoenzyme 3A4 (CYP3A4), the enzyme responsible for aprepitant metabolism. CYP3A4 at birth has negligible expression, and expression matures to approximately half of adult levels at 4 months of age, and reaches full maturity gradually over the next several years. Therefore, the dose adjustments used in older pediatric subjects are also appropriate for 4- to 6-month-olds, but should be reduced in subjects below 4 months of age to account for reduced metabolism. The proposed dose adjustment is to reduce the dose to half in subjects from 1 month up to 4 months of age, and reduce the dose to one fourth in subjects from birth to 1 month of age (Table 4). While no data currently

exist with aprepitant or fosaprepitant in this population to confirm this dose adjustment, data from a drug-drug interaction study in healthy adults co-administered ketoconazole and aprepitant is illustrative and included in the EMEND® product label. This approach will be verified with data from Protocol 029 for subjects birth to < 4 months old.

Subjects <12 years of age will NOT be permitted to participate in the current study until PK/PD and safety data from an ongoing PK/PD and safety study (MK-0517 Protocol 029) can be evaluated to confirm the planned dose adjustments for the subjects <12 years of age. Enrollment of subjects <12 years of age will begin once the study sites are notified of the final dosing instructions via a written letter from the SPONSOR.

4.2.2.2 Rationale for the Use of Ondansetron for Antiemetic Prophylaxis

IV ondansetron was chosen as the 5-HT_3 antagonist for Cycle 1 of this study since it has been extensively studied in the pediatric population and is approved for pediatric use. In clinical drug interaction studies, aprepitant did not have clinically important effects on the PK of ondansetron. As dosing information is not available in the U.S. label for pediatric subjects <6 months of age, the dose of IV ondansetron in this age group should be administered according to local standard of care. If ondansetron dosing for subjects less <6 months of age is not established locally, refer to the "Pediatric Oncology Group of Ontario (POGO) Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients" for guidance. Electronic source is available on the POGO website: http://www.pogo.ca/healthcare/practiceguidelines/.

In order to mitigate variability, IV ondansetron is required for Cycle 1 in this study and will be provided for prophylaxis use only by the Sponsor to be used **on days of emetogenic chemotherapy administration and up to 24 hours after chemotherapy**.

The prescribing information on Zofran® (ondansetron hydrochloride) injection for intravenous use [16] indicates in the Warnings and Precautions section that "ECG changes including QT interval prolongation have been seen in subjects receiving ondansetron", and recommend ECG monitoring in "subjects with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or subjects taking other medicinal products that lead to QT prolongation." As such, this study will exclude subjects with a known history of QT prolongation, congestive heart failure, bradyarrythmia, or subjects taking any medication that is known to lead to QT prolongation. Additional ECG monitoring will be performed for those subjects with an electrolyte abnormality (i.e., hypokalemia or hypomagnesemia) at baseline by including an ECG at 2 hours after the first dose of ondansetron in Cycle 1. It is advised that investigators should consider correction of known electrolyte abnormalities prior to administration of ondansetron, consistent with ondansetron labeling and local standards of care. Refer to the Zofran® for injection prescribing information for more details.

4.2.2.3 Rationale for Optional Corticosteroid Use for Antiemetic Prophylaxis

Dexamethasone is a corticosteroid that may be used for the prevention/treatment of CINV. As both aprepitant and dexamethasone are substrates of CYP3A4, the effect of aprepitant on oral dexamethasone PK was evaluated in one study (MK-0869 Protocol 041). In this study, the coadministration of aprepitant resulted in a significant 2-fold increase in dexamethasone AUC and C_{max}. A study evaluating the effects of aprepitant on the PK of IV dexamethasone has, likewise, demonstrated comparable results [17]. Thus, based upon available data, if dexamethasone is administered as part of the standard antiemetic regimen for subjects receiving fosaprepitant 150 mg (or age-based adjustment), the dose of dexamethasone should be reduced to 50% of the prescribed dose when administered within 48 hours following administration of fosaprepitant. This recommendation may be modified based on an ongoing pediatric PK study (Protocol 029) examining the interaction of dexamethasone and fosaprepitant in pediatric subjects birth to 1 years of age. If indicated, a revised dose adjustment will be implemented and sites will be notified via a written letter from the Sponsor about the change in the dose adjustment.

4.2.2.4 Rationale for Emetogenic Classification of Chemotherapeutic Agents

A schema that appropriately classifies the emetogenic risk of chemotherapy regimens is important for at least two reasons: (1) to provide a framework for treatment guidelines in the clinical setting, and (2) to precisely define the emetogenic challenge administered in a clinical trial. To address this need, a 4-level system that classifies chemotherapeutic agents by emetogenicity (high, moderate, low, and minimal) has been utilized by consensus groups in oncology, including ASCO, MASCC, the European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) [8-10; 18]. However, this system has been developed based on adult experience and cannot easily be extrapolated to the pediatric population due to potential differences in drug metabolism and susceptibility to nausea and vomiting [19-20].

The Pediatric Oncology Group of Ontario (POGO) developed pediatric guidelines of commonly used antineoplastic agents by emetogenicity [21]. This schema ranks single and multiple agent antineoplastic therapy as high emetic risk (>90%), moderate emetic risk (30-90%), low emetic risk (10-<30%) and minimal emetic risk (<10%) associated with the frequency of emesis in the absence of prophylaxis.

For this study, the classification criteria developed by POGO and endorsed by the Children's Oncology Group (COG) will be used as a guide for subject enrollment. Subjects who are administered a chemotherapeutic agent associated with moderate or high risk of emetogenicity based on the POGO criteria (see Section 12.5 – Emetogenicity of Commonly Used Chemotherapeutic Agents), or will be receiving a chemotherapeutic regimen that they have previously not been able to tolerate due to vomiting, will be eligible to enroll in this study. If a planned chemotherapy agent is not listed in the Emetogenicity of Commonly Used Chemotherapeutic Agents table, the investigator is encouraged to discuss the emetogenic stratification with the Clinical Director.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The efficacy endpoints assessed in the pediatric CINV studies were designed to capture different components of the symptoms associated with CINV. These include direct measurement of vomiting, retching and a surrogate measure of nausea (rescue medication use) with complete response defined as no vomiting, no retching, and no use of rescue medication. CINV has traditionally been measured in two distinct periods after the initiation of chemotherapy: the acute phase (0 to 24 hours) and the delayed phase (>24 to 120 hours). In order to assess the totality of the symptoms, the overall phase, which encompasses both phases over the 0 to 120 hour period, was also captured.

4.2.3.2 Pharmacokinetic Endpoints

To allow further characterization of aprepitant PK parameters in pediatric subjects, sparse PK samples will be collected in Optional Cycle 2.

Because of their comparatively smaller blood volumes, the opportunity to collect specimens for PK analyses in children is much more limited compared to adults. In order to limit the burden on these subjects, a flexible sparse sampling scheme will be utilized.

PK samples for aprepitant will be collected from all subjects participating in the optional Cycle 2 at two time points: Cycle 2, Day 1 at end of fosaprepitant infusion and 2 to 4 hours after completion of fosaprepitant infusion.

If the subject is still at the site or is returning to the site on Cycle 2 Days 2 or 3 (e.g., to receive additional chemotherapy), additional PK sample(s) will be collected at up to two additional time points: Cycle 2, Day 2 (ideally ~23 to 25 hours after fosaprepitant infusion on Cycle 2, Day 1); and Cycle 2, Day 3 (ideally ~46 to 50 hours after fosaprepitant infusion on Cycle 2, Day 1). Subjects who will not be at the site on Cycle 2, Days 2 and 3 do not need to return for PK sampling.

4.2.3.3 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA (buccal swab) specimens collected during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis

and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Based on the ongoing need for treatment options for the prevention of pediatric CINV, and the consistent efficacy and tolerability demonstrated by fosaprepitant and oral aprepitant in adults, the benefit-to-risk assessment for conducting MK-0517 Protocol 044 is favorable.

In completed and ongoing aprepitant and fosaprepitant studies in pediatric subjects in the development program (Protocols 097, 134, 208, 029), aprepitant/fosaprepitant was generally safe and well tolerated and the overall adverse experience profile for aprepitant/fosaprepitant has been similar to that reported previously in adult studies. Peripheral catheter infusion site reactions seen in the adult studies will not be an issue in this study due to the use of a central venous catheter for study drug administration.

The pediatric studies, which are designed to match the exposures of aprepitant and fosaprepitant in pediatric subjects to those in adults, have demonstrated a safety profile that is generally similar to that seen in prior clinical trials in adults. Thus, there is no expectation of increased safety risk for subjects enrolled in this study.

Beneficial effects of aprepitant have been seen in 2 pediatric trials. Efficacy was demonstrated in an aprepitant study in adolescents 12 to 17 years of age (Protocol 097) and a pediatric aprepitant study in patients 6 months to 17 years of age (Protocol 208). In these studies, a dose of aprepitant that approximated the demonstrated efficacious dose in adults provided better control of CINV over the control regimen. These data are described in the aprepitant Investigator's Brochure and support the conclusion that response to NK_1 blockade in children is similar to that in adults, and that matching systemic exposure between the adult and pediatric population is an appropriate approach for developing NK_1 antagonists (including aprepitant and its pro-drug fosaprepitant) for use in the pediatric CINV population.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the Investigators Brochure (IB) and Informed Consent and Assent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects between the ages of birth and 17 years (inclusive) with a documented malignancy who are scheduled to receive chemotherapeutic agent(s) associated with moderate or high risk of emetogenicity will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

5.1.2.1 Inclusion Criteria for Cycle 1

1. have parent/legal guardian (legally authorized representative) agreement to the subject's participation as indicated by parent/legal guardian signature on the informed consent form. Subject 12 to 17 years of age, or as required by local regulation, assents and has the ability to understand the nature and intent of the study including the ability to comply with study procedures, complete study diary, and is willing to keep scheduled study visits. The parent/legal guardian or subject may also provide consent/assent for Future Biomedical Research (FBR). However, the subject may participate in the main trial without participating in the FBR.

2. be 0 (at least 37 weeks gestation) to 17 years of age at time of randomization.

3. have a Lansky Play Performance score ≥60 (subjects ≤16 years of age) or a Karnofsky score ≥60 (subjects >16 years of age) as defined in Section 12.4 – Lansky and Karnofsky Performance Status Scales.

4. have a predicted life expectancy ≥3 months.

5. be receiving chemotherapeutic agent(s) associated with moderate or high risk of emetogenicity for a documented malignancy, or a chemotherapy regimen not previously tolerated due to vomiting. See Section 12.5 – Emetogenicity of Commonly Used Chemotherapeutic Agents, for guidance on the classification of chemotherapeutic agents.

   Cycle 1 only: If a subject's chemotherapy regimen has multiple chemotherapies with different emetogenic potential, then the most emetogenic agent must be part of the Day 1 regimen.

6. have a preexisting functional central venous catheter available for study drug administration.

7. meet one of the following categories:

a) The subject is a male.

b) The subject is a female who is not of reproductive potential, defined as a female who either: (1) has not begun menses; (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.

c) The subject is a female who is of reproductive potential and agrees to avoid becoming pregnant[#] in the 28 days prior to receiving study drug, while receiving study drug and for at least 30 days (or local standard of care if longer) after the last dose of study drug (including the optional cycles) by complying with one of the following: (1) practice abstinence[†] from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- non-hormonal intrauterine device (IUD)
- vasectomy of a female subject's male partner

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive (oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection); subjects must agree to add a barrier form of contraception during treatment with and for 1 month following the last dose of fosaprepitant (or local standard of care if longer).

[#] Female of child bearing potential is required to have a negative pregnancy test prior to start of fosaprepitant dosing in a cycle.

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

5.1.2.2 Inclusion Criteria for Optional Cycles 2 to 6

In order to be eligible for participation in an optional cycle, the subject must meet inclusion criteria 5, 6, and 7 above in addition to the two criteria below.

8. have completed the preceding study cycle and related study procedures satisfactorily, have no unresolved drug related adverse events and continued participation in an optional cycle poses no unwarranted risk to the subject as determined by the investigator.

9. have parent/legal guardian (legally authorized representative) or subject (if subject is 18 years old) agreement to the subject's participation as indicated by parent/legal guardian or subject (if subject is 18 years old) signature on the informed consent form for the optional cycles. Subject 12 to 17 years of age, or as required by local regulation, assents and has the ability to understand the nature and intent of the study including the ability to comply with study procedures and is willing to keep scheduled study visits.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

5.1.3.1 Exclusion Criteria for Cycle 1 Only

1. has vomited in the 24 hours prior to chemotherapy initiation on Treatment Day 1.

2. has a symptomatic primary or metastatic central nervous system (CNS) malignancy with nausea and/or vomiting. Subject who is asymptomatic is allowed to participate.

3. has abnormal laboratory values as follows:

    - peripheral absolute neutrophil count (ANC) <1000/mm^3
    - platelet count <75,000/mm^3
    - aspartate aminotransferase (AST) >5.0 x upper limit of normal (ULN) for age
    - alanine aminotransferase (ALT) >5.0 x ULN for age
    - bilirubin >1.5 x ULN for age
    - creatinine >1.5 x ULN for age

4. will be receiving stem cell rescue therapy in conjunction with study related course of emetogenic chemotherapy or during the 14 days following administration of fosaprepitant/placebo for fosaprepitant.

5. has received or will receive total body irradiation or radiation therapy to the abdomen (includes the level of the diaphragm and below) or pelvis in the week prior to Treatment Day 1 and/or during the diary reporting period (120 hours following initiation of chemotherapy).

6. has had benzodiazepine (potential to alleviate nausea and vomiting), opioid or opioid like (e.g., tramadol hydrochloride) therapy (potential to enhance nausea and vomiting) initiated within 48 hours prior to study drug administration, or is expected to receive within 120 hours following initiation of chemotherapy, except for single daily doses of midazolam, temazepam or triazolam.

    - Continuation of chronic benzodiazepine, opioid or opioid like therapy is permitted provided it was initiated at least 48 hours prior to study drug administration.

7. has been started on systemic corticosteroid therapy within 72 hours prior to study drug administration or is expected to receive a corticosteroid as part of the chemotherapy regimen.

    Exceptions:

    - subject who is receiving chronic (>72 hours), daily steroid therapy can be enrolled provided the steroid dose is not >0.14 mg/kg (up to 10 mg) of prednisone daily or equivalent.

    - for supportive care, subject is permitted to receive a single dose of corticosteroid within 3 days prior (but not on the day of study drug administration) provided it is less than the equivalent of 20 mg of prednisone.

8. is currently taking, or has taken within 48 hours of Treatment Day 1 the following drugs with antiemetic properties: 5-HT3 antagonists (e.g., ondansetron), benzamides (e.g., metoclopramide), butyrophenones (e.g., haloperidol), cyclizine, domperidone, herbal therapies with potential antiemetic properties, olanzapine, phenothiazines (e.g., prochlorpenzine), scopolamine. Note: This is not an exhaustive list. The Sponsor should be consulted in individual cases where the subject is taking an antiemetic not listed above.

5.1.3.2 Exclusion Criteria for Cycle 1 <u>and</u> Optional Cycles 2 to 6

9. is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

10. is currently a user of any recreational or illicit drugs (including marijuana) or has current evidence of drug or alcohol abuse or dependence as determined by the investigator.

11. is mentally incapacitated or has a significant emotional or psychiatric disorder that, in the opinion of the investigator, precludes study entry.

12. is pregnant or breast feeding.

13. is allergic to fosaprepitant, aprepitant, ondansetron, or any other 5-HT_3 antagonist.

14. has a known history of QT prolongation or is taking any medication that is known to lead to QT prolongation. A list of many drugs known to cause QT prolongation will be provided in a separate document in the Investigator Trial File Binder (or equivalent). This may not be a comprehensive list.

15. has an active infection (e.g., pneumonia), congestive heart failure, bradyarrythmia, any uncontrolled disease (e.g., diabetic ketoacidosis, gastrointestinal obstruction) except for malignancy, or has any illness which in the opinion of the investigator, might confound the results of the study or pose unwarranted risk in administering study drug or concomitant therapy to the subject.

16. has ever participated in a previous study of aprepitant or fosaprepitant or has taken a non-approved (investigational) drug within the last 4 weeks. **Note:** Subjects in investigational studies with marketed chemotherapeutic agents (whether explicitly for children or only marketed for adults and usually administered in children with the appropriate dose adjustments) are allowed to enroll if they fulfill all other entry criteria. Previous or current participation in an observational study is acceptable.

17. has received any medication within the timeframes listed in Table 1 or needs to receive any medication listed in Table 1 during the time period specified relative to initiation of chemotherapy.

    Note: The list of CYP3A4 medications listed in Table 1 is not exhaustive. The Sponsor should be consulted in individual cases where the subject is taking a moderate to strong CYP3A4 inducer/substrate/inhibitor (not including chemotherapy agents) not listed in Table 1.

Table 1 Other Excluded Medications

	Subject is **currently taking**, or has taken within **30 days** of Treatment Day 1 or is expected to receive within **120 hours** following initiation of chemotherapy	Subject is **currently taking**, or has taken within **7 days** of Treatment Day 1 or is expected to receive within **120 hours** following initiation of chemotherapy	Subject is **currently taking** or is expected to receive within **2 weeks** following initiation of chemotherapy
CYP3A4 Inducers	barbiturates, carbamazepine, phenytoin, rifampicin, rifabutin, St. John's Wort		
CYP3A4 Substrates		amifostine, astemizole, cisapride, marinol, pimozide, terfenadine	
CYP3A4 Inhibitors[A]		amprenavir, aprepitant, atazanavir, boceprevir, ciprofloxacin, clarithromycin, conivaptan, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole	
CYP2C9 Substrates			warfarin
[A]Azithromycin is a macrolide antibiotic that is permitted during the study period.			

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 2 and Table 3.

Table 2 Trial Treatments – Cycle 1

Drug	Dose/Potency	Dose Frequency	Route of Administration	Treatment Period	Use
fosaprepitant	150 mg or age-based adjustment	single dose	IV	Day 1	experimental
placebo for fosaprepitant (normal saline)	0 mg	single dose	IV	Day 1	placebo
ondansetron	per product label or standard of care	one dose prior to chemotherapy infusion required, then per product label or standard of care	IV	Day 1 and at investigator's discretion on the day(s) of chemotherapy and up to 24 hours after chemotherapy	standard of care/ prophylaxis
dexamethasone (optional)	per product label or standard of care *	per product label or standard of care	IV	at investigator's discretion on the day(s) of chemotherapy and up to 24 hours after chemotherapy	prophylaxis
* For subjects receiving fosaprepitant, the dose of dexamethasone should be reduced to 50% of the prescribed dose when administered within 48 hours following administration of fosaprepitant. Dose reduction applies to both dexamethasone used prophylactically and as rescue medication. No dose adjustment to dexamethasone will be made for subjects receiving placebo for fosaprepitant.					

Table 3 Trial Treatments – Cycles 2 to 6

Drug	Dose/Potency	Dose Frequency	Route of Administration	Treatment Period	Use
fosaprepitant	150 mg or age-based adjustment	single dose	IV	Day 1	experimental
5-HT_3 antagonist	per product label or standard of care	one dose prior to chemotherapy infusion required, then per product label or standard of care	any route of administration	Day 1 and per product label or standard of care	standard of care/ prophylaxis
dexamethasone (optional)	per product label or standard of care *	per product label or standard of care	at investigator's discretion	at investigator's discretion	prophylaxis
* The dose of dexamethasone should be reduced to 50% of the prescribed dose when administered within 48 hours following administration of fosaprepitant. Dose reduction applies to both dexamethasone used prophylactically and as rescue medication.					

Trial treatment should begin on the day of randomization or as close as possible to the date on which the subject is allocated/assigned.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

5.2.1.1.1 Fosaprepitant – Cycle 1 (Treatment Group 1) and Optional Cycles 2 to 6

Open-label fosaprepitant (MK-0517) will be supplied by the Sponsor as a 150-mg vial of lyophilized powder. The site will supply its own source of normal saline to be utilized in the preparation of fosaprepitant. It will be prepared in Cycle 1 in a blinded manner by an unblinded pharmacist or qualified trial site personnel. Subjects in Treatment Group 1 of Cycle 1 and those subjects participating in an optional, open-label cycle will receive 150 mg (or age-based dose adjustment not to exceed 150 mg) of fosaprepitant. The individual fosaprepitant doses for each age group are summarized in Table 4 – Fosaprepitant Dose for Each Age Group.

The age-based dosing for subjects birth to <12 years of age may be modified, as needed, based on PK, efficacy and/or safety/tolerability data from Protocol 029, and/or based on input from regulatory health authorities. If indicated, a revised dose adjustment will be implemented and sites will be notified via a written letter from the Sponsor if there are changes to the age-specific dose.

Table 4 Fosaprepitant Dose for Each Age Group

Age-Specific Dose Adjustments*					
0-<2 years			2 to < 6 years	6 to <12 years	12 to 17 years
0 to <1 month	1 to < 4 months	4 months to <2 years			
1.25 mg/kg	2.5 mg/kg	5.0 mg/kg	5.0 mg/kg	5.0 mg/kg	150 mg
* not to exceed 150 mg					

Specific instructions on the preparation of fosaprepitant will be provided in a separate document. **Note:** Fosaprepitant is incompatible with any solutions containing divalent cations (e.g., Ca^{++}, Mg^{++}), including Lactated Ringer's Solution and Hartmann's Solution.

5.2.1.1.2 Placebo for fosaprepitant (normal saline) – Cycle 1 (Treatment Group 2)

Subjects in the control regimen (Treatment Group 2) will receive placebo for fosaprepitant (normal saline). To maintain blinding, placebo for fosaprepitant will be prepared in a blinded manner by the unblinded study pharmacist or qualified trial site personnel. The placebo for fosaprepitant will be prepared using a volume of normal saline matching the volume that would be used to prepare fosaprepitant as detailed in Table 4 – Fosaprepitant Dose for Each Age Group. The site will supply its own source of normal saline to be utilized as placebo for fosaprepitant.

Specific instructions on the preparation of placebo for fosaprepitant will be provided in a separate document.

5.2.1.1.3 Ondansetron (both treatment groups) - Cycle 1

Ondansetron is the only 5-HT_3 antagonist that may be used as part of the preventative antiemetic regimen in Cycle 1. IV ondansetron is required for Cycle 1 of this study and will be supplied for prophylaxis use only by the Sponsor to be used on days of chemotherapy administration and up to 24 hours after chemotherapy.

Ondansetron will be prepared per product label or based on local standard of care not to exceed the maximum single dose specified for pediatric use.

5.2.1.1.4 5-HT_3 Antagonist – Optional Cycles 2 to 6

Any 5-HT_3 antagonist may be used as part of the preventative antiemetic regimen in Cycles 2 to 6. The 5-HT_3 antagonist will be supplied by the study site.

The 5-HT_3 antagonist will be prepared per product label or based on local standard of care not to exceed the maximum single dose specified for pediatric use.

5.2.1.1.5 Dexamethasone (optional) - Cycle 1 and Optional Cycles 2 to 6

Dexamethasone may be administered as part of the antiemetic regimen at the discretion of the investigator. In Cycle 1, it can be used prophylactically only on days of chemotherapy administration and up to 24 hours after chemotherapy. If dexamethasone is used, it will be supplied locally by the study site. In Cycle 1, IV dexamethasone must be used and prepared by the unblinded pharmacist or qualified trial site personnel to allow for dose reduction and to maintain the blind. In Cycles 2 to 6, other dosage forms can be used as long as the dosage form can be reduced appropriately (see dose reduction below).

For any subject receiving fosaprepitant, whether receiving the full dose or an age-based adjustment, the dose of dexamethasone should be reduced to 50% of the prescribed dose when administered within 48 hours following administration of fosaprepitant. No dose adjustment of dexamethasone will be made for subjects allocated to the control regimen in Cycle 1.

Cycle 1 only

In order to maintain the study blind during Cycle 1, the unblinded pharmacist or qualified trial site personnel should ensure that dexamethasone is prepared in a manner that maintains masking of the drug dose and allows for the site personnel administering the corticosteroid to remain blinded. For this study, unblinded Merck personnel will be designated to work with the unblinded pharmacist or qualified trial site personnel as needed.

An unblinded pharmacist or qualified trial site personnel is required for Cycle 1 only.

Note: The dose adjustment recommendation for IV dexamethasone in subjects birth to 1 year of age receiving fosaprepitant may be modified, as needed, based on an ongoing pediatric pharmacokinetic study (Protocol 029) examining the interaction of dexamethasone and fosaprepitant in pediatric subjects. If indicated, a revised dose adjustment will be implemented and sites will be notified via a written letter from the Sponsor about the change in the dose adjustment.

5.2.2 Timing of Dose Administration

5.2.2.1 Fosaprepitant/Placebo for Fosaprepitant

Age 0 to <12 years: At approximately 90 minutes prior to initiation of the first emetogenic chemotherapy, subjects will be administered fosaprepitant or placebo, via a central venous

catheter, over a period of approximately 60 minutes. The infusion will be complete approximately 30 minutes prior to chemotherapy initiation.

The use of a longer infusion time for the younger children is to mitigate the predicted higher C_{max} to AUC ratio in young children compared to adults. It is expected that extending the infusion duration to 60 minutes for these younger children (<12 years of age) would reduce the predicted peak aprepitant concentrations to levels similar to that of adults.

Age 12 to 17 years: At approximately 60 minutes prior to initiation of the first emetogenic chemotherapy, subjects will be administered fosaprepitant or placebo, via a central venous catheter, over a period of approximately 30 minutes. The infusion will be complete approximately 30 minutes prior to chemotherapy initiation.

5.2.2.2 Ondansetron - Cycle 1

Ondansetron will be administered per product label or based on local standard of care. For subjects 6 months to 17 years old, the first dose on Day 1 should be no later than 30 minutes prior to initiation of the first emetogenic chemotherapy. The timing of the first dose of ondansetron administration for subjects <6 months old should be scheduled according to local standard of care. Additional doses of IV ondansetron on Day 1 should be administered according to local standard of care.

Subjects receiving multi-day chemotherapy regimens are permitted to receive preventative antiemetic treatment with IV ondansetron after Day 1, with or without IV dexamethasone, if clinically indicated and consistent with local standard of care; however, **only on the day(s) of chemotherapy administration and up to 24 hours after chemotherapy**.

5.2.2.3 5-HT_3 Antagonist - Optional Cycles 2-6

The 5-HT_3 antagonist will be administered per product label or local standard of care with the first dose administered prior to initiation of chemotherapy.

5.2.2.4 Dexamethasone (optional) - Cycle 1 and Optional Cycles 2 to 6

Dexamethasone will be administered per product label or local standard of care. In Cycle 1 it should be administered intravenously no later than 30 minutes prior to initiation of the first emetogenic chemotherapy. Subjects receiving multi-day chemotherapy regimens are permitted to receive preventative antiemetic treatment with IV dexamethasone after Day 1, if clinically indicated and consistent with local standard of care; however, **only on the day(s) of chemotherapy administration and up to 24 hours after chemotherapy**. In optional Cycles 2 to 6, dexamethasone may be administered as part of an anti-emetic regimen based on local standard of care.

See section 5.2.1.1.5, Dexamethasone (optional) - Cycle 1 and Optional Cycles 2 to 6, for dose reduction instructions.

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. Fosaprepitant, placebo for fosaprepitant and dexamethasone (if prescribed) in Cycle 1 will be prepared and dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel who are not involved in the treatment or clinical evaluation of the subjects. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to fosaprepitant + ondansetron or placebo for fosaprepitant + ondansetron respectively once the answers to the stratification questions defined below are provided to the system. See Section 7.1.1.7, Assignment of Randomization Number, for additional details on the assignment of the randomization number.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. Age on Day 1 of emetogenic chemotherapy in Cycle 1 (0 to <2 years, 2 to <6 years, 6 to <12 years, 12 to 17 years).

2. Planned use of a chemotherapy agent associated with High Risk of emetogenicity in Cycle 1 (Yes or No).

3. Planned use of dexamethasone as an antiemetic in Cycle 1 (Yes or No).

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

If there is a clinical indication for any medication specifically prohibited during the trial, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy requires the mutual agreement of the investigator, and the Sponsor, and the subject/parent/legal guardian.

Listed below are specific restrictions for concomitant therapy during the course of the trial:

1. A list of medications that are prohibited prior to and during the trial are identified in Section 5.1.3. Subject Exclusion Criteria.

2. No drug or herbal therapy of any type is to be initiated during a study cycle without the knowledge of the investigator, unless required to treat an adverse event.

5.6 Rescue Medications & Supportive Care

Rescue medication is defined as any medication used to relieve symptoms of established nausea or vomiting. The definition of rescue medication will be explained to the subject/parent/caregiver. Rescue medication should not be taken to prevent nausea or vomiting. Continuous administration of rescue antiemetic medications such as via a transdermal patch is not permitted. Subjects will be instructed that they are allowed to take rescue medication if needed for established nausea or vomiting.

In Cycle 1, subjects will be provided with a prescription for rescue medication according to investigator preference. Permitted rescue medications are:

- 5-HT_3 antagonists (dolasetron, granisetron, ondansetron, palononsetron or tropisetron)
- Benzamides (e.g., alizapride or metoclopramide)
- Benzodiazepines
- Butyrophenones (e.g., droperidol or haloperidol)
- Cannabinoids (e.g., nabilone)
- Cyclizine
- Dexamethasone*
- Domperidone
- Herbal therapies with potential antiemetic properties
- Methylprednisolone
- Phenothiazines (e.g., chlorpromazine, fluphenazine, perphenazine, prochlorperazine, or thiethylperazine)
- Scopolamine

The Patient Diary will be used to record the date, time, and type of rescue medication used during Cycle 1.

In optional Cycles 2 to 6, the subject can be provided with a prescription for rescue medication according to investigator preference.

* If dexamethasone is used as rescue medication in Cycle 1, IV dexamethasone must be used and prepared by the unblinded pharmacist or qualified trial site personnel to allow for dose reduction and to maintain the blind. In Cycles 2 to 6, other dosage forms can be used as long as the dosage form can be reduced appropriately (see dose reduction below).

For any subject receiving fosaprepitant, whether receiving the full dose or an age-based adjustment, the dose of dexamethasone should be reduced to 50% of the prescribed dose when administered within 48 hours following administration of fosaprepitant.

5.7 Diet/Activity/Other Considerations

There are no diet or activity restrictions.

5.8 Subject Withdrawal/Discontinuation Criteria

Subject/parent/legal guardian may withdraw consent and/or assent (as applicable) at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Discontinuation from treatment is "permanent". Once a subject is discontinued, he/she shall not be allowed to restart treatment.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject withdraws assent.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.
- The subject has a positive pregnancy test. The pregnancy will be followed to resolution.

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- Pregnancy
- Any drug-related serious AE (SAE) or any SAE which might affect the ability of the subject to safely continue in the trial or provide reliable efficacy measurements.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject/parent/legal guardian signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

Cycle 1 Study Day and Time are relative to initiation of the first emetogenic chemotherapy infusion (T_{zero}).					
Trial Period	Screening	Treatment		Post-Treatment	
Visit Number/Title:	1 Screening	2 Randomization	Telephone/ Direct Contact	3 Post-Treatment	4 Follow-Up/ Discontinuation
Study Day	-28 to 1 [A]	1	2 to 5 [B]	6 to 9 [C]	15 to 20 [C]
Administrative Procedures					
Informed Consent and Assent (if applicable)	X [D]				
Informed Consent and Assent (if applicable) for Future Biomedical Research	X [E]				
Inclusion/Exclusion Criteria	X	X			
Subject Identification Card	X (dispense)				X (collect) [F]
Medical History	X	X			
Prior Medication Review	X	X			
Concomitant Medication Review		X		X	X
Register Study Visit/Assignment of Screening & Randomization Numbers and/or Dispense Study Therapy via IVRS/IWRS	X	X			X [G]
Patient Diary Education for Subject/Parent/Caregiver and dispense diary		X [H]			
Laboratory and/or ECG Safety Test Review	X	X			X
Rescue Medication Prescription		X			
Subject/Parent/Caregiver Diary Completion		X----------		----------X	
Telephone/Direct Contact (scripted questions)			X [B]	X [B]	
Patient Diary Review/Collection (with Subject/Parent/Caregiver)				X	
Clinical Procedures/Assessments					
Full Physical Examination	X [I]				
Directed Physical Examination					X
Height		X			
Weight		X			
Vital Signs (blood pressure, heart rate, respiratory rate, axillary/oral/ rectal/temporal/tympanic temperature)	X	X [J]		X	X
12-Lead Electrocardiogram (ECG)	X [K]	X [L]			X
Lansky or Karnofsky Performance Status Evaluation	X				
Fosaprepitant or Matching Placebo Administration		X [M]			
IV Ondansetron Administration		X [N]			
Optional Dexamethasone Administration		X [O]			
Chemotherapy Infusion		X [P]			
Adverse Event Monitoring	X----------				----------X

Cycle 1 Study Day and Time are relative to initiation of the first emetogenic chemotherapy infusion (T_{zero}).					
Trial Period	Screening	Treatment		Post-Treatment	
Visit Number/Title:	1 Screening	2 Randomization	Telephone/ Direct Contact	3 Post-Treatment	4 Follow-Up/ Discontinuation
Study Day	-28 to 1 [A]	1	2 to 5 [B]	6 to 9 [C]	15 to 20 [C]
Laboratory Procedures/Assessments					
Laboratory Safety Evaluations (Hematology, Chemistry)	X [K]				X
Ionized Calcium evaluation	X [Q]	X [Q]			
Urine Pregnancy Test – if applicable	X [KR]				
Buccal swab samples for Future Biomedical Research		X [S]			

[A] The Screening and Randomization visits can occur on the same day as long as all study procedures are completed and subject eligibility is confirmed.

[B] Telephone or direct contact must be made daily on Days 2, 3, 4, and 5. Telephone/direct contact must also be made on Day 6 if the Post Treatment visit is not on Day 6.

[C] One visit occurs during the designated period of study days. The Follow-Up Visit can be scheduled to coincide with the start of the next study cycle provided that the next round of chemotherapy is 14-19 days after Treatment Day 1 (study days 15 to 20).

[D] Informed consent/assent MUST be obtained prior to any Visit 1 procedures.

[E] Subject participation in Future Biomedical Research is optional.

[F] A reasonable attempt should be made to collect the Subject Identification Card if subject discontinues during Cycle 1 or if subject is not participating in optional cycle(s).

[G] Register study discontinuation visit in IVRS/IWRS if subject discontinues during Cycle 1 or if subject is not participating in optional cycle(s).

[H] The Subject/Parent/Caregiver should be educated on the use of the Patient Diary prior to the start of emetogenic chemotherapy.

[I] Full physical exam (excluding breast, rectal, and urogenital, unless clinically indicated).

[J] All vital sign measurements will be obtained prior to fosaprepitant infusion. Blood pressure and heart rate will be measured again ~ 15 minutes after completion of fosaprepitant infusion, prior to the start of chemotherapy.

[K] ECG, Laboratory Safety Evaluations and Urine Pregnancy Test must be completed within 7 days prior to initiation of study medication. See Section 7.1.3.1 – Local Laboratory Safety Evaluations for the list of Laboratory Tests.

[L] This ECG is obtained ~2 (no later than 3) hours after initial administration of IV ondansetron in those subjects with a baseline potassium and/or magnesium level below the normal range for the subject's age.

[M] Fosaprepitant or matching placebo dose is initiated at ~90 minutes prior to initiation of the first emetogenic chemotherapy and administered via a central venous catheter over a period of ~60 minutes for subjects <12 years old and ~60 minutes prior to initiation of the first emetogenic chemotherapy and administered over a period of ~30 minutes for subjects 12 to 17 years old. The infusion will be complete ~30 minutes prior to chemotherapy initiation.

[N] IV ondansetron is required for Cycle 1 and will be supplied for prophylaxis use only by the Sponsor to be used on days of chemotherapy administration and up to 24 hours after chemotherapy. For subjects 6 months to 17 years old, the first dose on Day 1 should be no later than 30 minutes prior to initiation of the first emetogenic chemotherapy. The timing of the first dose of ondansetron administration for subjects <6 months old should be scheduled according to local standard of care. Additional doses of IV ondansetron on Day 1 should be administered according to local standard of care. For multi-dose chemotherapy regimens, IV ondansetron can be administered on subsequent days if clinically warranted and per local standard of care; however, it should only be administered on the day(s) of chemotherapy administration and up to 24 hours after chemotherapy administration.

[O] IV dexamethasone may be administered as part of an anti-emetic regimen based on local standard of care, but no later than 30 minutes prior to initiation of the first emetogenic chemotherapy. For subjects receiving fosaprepitant, the dose of dexamethasone should be reduced to 50% of the prescribed dose when administered within 48 hours following administration of fosaprepitant. Dose reduction applies to dexamethasone used prophylactically and as rescue medication. No dose adjustment will be made for subjects receiving placebo for fosaprepitant. For multi-dose chemotherapy regimens, IV dexamethasone can be administered on subsequent days if clinically warranted and per local standard of care; however, it should only be administered on the day(s) of chemotherapy administration and up to 24 hours after chemotherapy administration.

[P] The time of initiation of the first emetogenic chemotherapy infusion will be recorded by the site staff on the front page of the Patient Diary. This date and time will be designated as T_{zero} (0 hour) for the study cycle.

[Q] At selected sites, blood samples for ionized calcium will be drawn at the screening visit and at the randomization visit ~15 minutes after completion of fosaprepitant/placebo infusion, prior to the start of chemotherapy.

[R] Applies to female subjects of reproductive potential only. If a female subject reaches menarche (menstruates for the first time), a urine pregnancy test must be done. Post-menarche female subjects must have a negative urine pregnancy test at Screening. Results must be obtained prior to study drug administration. Urine pregnancy testing should be repeated at subsequent visits if the subject reports non-compliance to birth control methods, if there is a question about potential pregnancy or as required by local guidelines. **Note:** a serum pregnancy test can be performed instead of the urine test per local regulatory requirements or standard of care.

[S] Informed consent/assent for future biomedical research must be obtained before the buccal swab DNA samples are collected. The buccal swab DNA samples should be obtained predose on Day 1, on randomized subjects only, or at a later date as soon as the informed consent/assent is obtained.

Cycles 2-6 Study Day and Time are relative to initiation of the first emetogenic chemotherapy infusion (T_{zero}).		
Trial Period	Treatment	Post-Treatment
Visit Title:	Treatment	Follow-Up/ Discontinuation
Study Day	1	15 to 20[A]
Administrative Procedures		
Informed Consent and Assent (if applicable)	X[B]	
Inclusion/Exclusion Criteria	X	
Subject Identification Card		X (collect) [C]
Concomitant Medication Review	X	X
Register Study Visit and/or Dispense Study Therapy via IVRS/IWRS	X	X[D]
Rescue Medication Prescription (optional)	X	
Clinical Procedures/Assessments		
Directed Physical Examination	X	X
Weight	X	
Vital Signs (blood pressure, heart rate, respiratory rate, axillary/oral/rectal/temporal/tympanic temperature)	X[E]	X
Fosaprepitant Administration	X[F]	
5-HT_3 Antagonist Administration	X[G]	
Optional Dexamethasone Administration	X[H]	
Chemotherapy Infusion	X	
Adverse Event Monitoring	X----------X	
Laboratory Procedures/Assessments		
Urine Pregnancy Test – if applicable	X[IJ]	
Pharmacokinetic (PK) Evaluations (**Cycle 2 Only**)	X[K]	

[A] One visit occurs during the designated period of study days. The Follow-Up Visit can be scheduled to coincide with the start of the next chemotherapy cycle provided that the next round of chemotherapy is 14-19 days after Treatment Day 1 (study days 15 to 20) of the current chemotherapy cycle.

[B] Informed consent/assent MUST be obtained prior to any procedures being performed in Cycle 2.

[C] A reasonable attempt should be made to collect the Subject Identification Card when subject discontinues/completes the study.

[D] Register study discontinuation visit when subject discontinues from the study.

[E] All vital sign measurements will be obtained prior to fosaprepitant infusion. Blood pressure and heart rate will be measured again ~ 15 minutes after completion of fosaprepitant infusion, prior to the start of chemotherapy.

[F] Fosaprepitant dose is initiated at ~90 minutes prior to initiation of the first emetogenic chemotherapy and administered via a central venous catheter over a period of ~60 minutes for subjects <12 years old and ~60 minutes prior to initiation of the first emetogenic chemotherapy and administered over a period of ~30 minutes for subjects 12 to 17 years old. The infusion will be complete ~30 minutes prior to chemotherapy initiation.

[G] The 5-HT_3 antagonist will be supplied by the Site and will be administered per product label or local standard of care prior to initiation of the first emetogenic chemotherapy.

[H] Dexamethasone may be administered as part of an anti-emetic regimen based on local standard of care. The dose of dexamethasone should be reduced to 50% of the prescribed dose when administered within 48 hours following administration of fosaprepitant. Dose reduction applies to dexamethasone used prophylactically and as rescue medication.

[I] Urine Pregnancy Test must be completed within 7 days prior to initiation of study medication.

[J] Applies to female subjects of reproductive potential only. If a female subject reaches menarche (menstruates for the first time), a urine pregnancy test must be done. Results must be obtained prior to study drug administration. Urine pregnancy testing should be repeated at subsequent visits if the subject reports non-compliance to birth control methods, if there is a question about potential pregnancy or as required by local guidelines. **Note:** a serum pregnancy test can be performed instead of the urine test per local regulatory requirements or standard of care.

[K] **Cycle 2 Only:** PK samples for aprepitant to be collected from all subjects at two time points: Cycle 2, Day 1 at end of fosaprepitant infusion and 2 to 4 hours after (completion) of fosaprepitant infusion. If the subject is still at the site or is returning to the site on Cycle 2 Days 2 or 3 (e.g., to receive additional chemotherapy), additional PK sample(s) will be collected at up to two additional time points: Cycle 2, Day 2 (ideally ~23 to 25 hours after fosaprepitant infusion on Cycle 2, Day 1); and Cycle 2, Day 3 (ideally ~46 to 50 hours after fosaprepitant infusion on Cycle 2, Day 1). Subjects who will not be at the site on Cycle 2, Days 2 and 3 do not need to return for PK sampling

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent and/or assent (if applicable) be obtained from the subject/parent/legal guardian. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent/Assent

The investigator or qualified designee must obtain documented consent and/or assent (if applicable) from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent/Assent

Consent/assent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent/assent form should be given to the subject before participation in the trial.

The initial informed consent/assent form, any subsequent revised written informed consent/assent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent/assent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements. The assent, as applicable, will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent and/or assent (if applicable) to the subject/parent/legal guardian, answer all of his/her questions, and obtain written informed consent and/or assent (if applicable) before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent/assent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card (Clinical Trial Identification Card)

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject/parent/legal guardian provides written informed consent and/or assent, as applicable.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Specific medical history information will be reviewed and documented prior to treatment and will include:

- Date/type of cancer diagnosis
- History of CINV
- History of motion sickness
- History of morning sickness during pregnancy, if applicable
- History of QT prolongation
- Allergies to fosaprepitant aprepitant, ondansetron, or any other 5-HT_3 antagonist

- All active conditions
- All inactive conditions diagnosed within the previous 5 years

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review and record prior medication taken by the subject in the preceding 30 days prior to entering the study. The doses will not be recorded. For subjects hospitalized during this period, only the discharge medications will be recorded.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject starting on Day 1 of a study cycle through 14 days following the dose of fosaprepitant/placebo for fosaprepitant. This will include the name of the medication, date(s) of use and reason for use. In addition, for chemotherapy medications, the dose will be recorded along with the start and stop times of chemotherapy.

A list of medications that are prohibited prior to and during the trial are identified in Section 5.1.3. Subject Exclusion Criteria. If there is a clinical indication for any medications specified in Section 5.1.3, refer to Section 5.5 Concomitant Medications/Vaccinations for further guidance.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

The subject identification card will be updated with the screening number.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.1 - Screening.

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 randomization number.

After all required study screening procedures have been completed and subject's eligibility has been confirmed, the randomization visit will be registered in IVRS/IWRS.

The subject identification card will be updated with the randomization number.

The date of treatment assignment should generally correspond to the date of randomization. However, for investigational sites unable to logistically prepare the fosaprepitant/placebo for fosaprepitant on Day 1 that have obtained written permission from the Sponsor to prepare the fosaprepitant/placebo for fosaprepitant on Day -1, the date of study medication administration will differ from the date of IVRS/IWRS treatment assignment. If the fosaprepitant is prepared on Day -1, the timing of the fosaprepitant administration must be carefully monitored to ensure it is administered to the subject within 24 hours of preparation since reconstituted fosaprepitant may become unstable after 24 hours.

Sites contacting the IVRS/IWRS on Day -1 must verify and document that the subject continues to meet the eligibility criteria before administering the first dose of assigned study medication on Day 1.

7.1.1.8 Trial Compliance (Study Medication/Patient Diary)

Administration of fosaprepitant/placebo for fosaprepitant will be witnessed by the investigator and/or trial staff. The total volume of fosaprepitant infused will be compared to the total volume prepared to determine compliance with study dosing.

The site staff will give the subject/parent/caregiver a paper Patient Diary at the Randomization Visit. Sites will be trained on the use of the diary by the Sponsor and are expected to subsequently train the subject/parent/caregiver on how to complete the diary. To ensure ongoing subject compliance with diary reporting, site staff will contact the subject/parent/caregiver on Days 2 to 5 and on Day 6, if the subject's post-treatment visit is not scheduled for that day, to remind him/her to record episodes of vomiting/dry heaves and use of medication for vomiting or nausea in the Patient Diary. The site staff will review the Patient Diary in detail with the subject/parent/caregiver at the Post-Treatment Visit.

Interruptions from the protocol specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.1.9 Patient Diary Education for Subject/Parent/Caregiver - Cycle 1 Only

At the Randomization Visit, the subject/parent/caregiver will be given one diary for the use in pediatric subjects (birth to <12 years) or one for use in adolescent subjects (12 to 17 years). The diaries are identical except that the pediatric diary poses efficacy questions and provides instructions for completion to the subject's parent/caregiver whereas the adolescent diary poses the questions and provides instructions for completion to the subject. The diaries

will collect rescue medications and vomiting episodes for a 5-day period (120 hours), starting on Day 1.

Assessment of efficacy will begin at the initiation of the first emetogenic chemotherapy infusion (T_{zero}) and will end 120 hours later. Efficacy will be assessed in Cycle 1 only using the Patient Diary.

The site staff will instruct the subject/parent/caregiver on the use of the Patient Diary by reviewing the "Instructions for Completing This Diary" page with the subject/parent/caregiver ensuring he/she understands the definitions for vomiting and dry heaves. In addition, the subject/parent/caregiver should be told that nausea is defined as "feeling the need to vomit". Distinct vomiting episodes are, by definition, separated by the absence of vomiting or dry heaves for at least one minute. The subject/parent/caregiver will be instructed to record the date and time of any episodes of vomiting/dry heaves and use of any medication for vomiting or nausea in the diary at the time the episode occurs or the medication is taken.

The site staff will complete the shaded areas of the diary. The subject/parent/caregiver will record each time the subject vomits, has dry heaves or has to take medication for vomiting or nausea. Subjects (or their parent/caregiver) must continue to fill out the diary even if the subject has episodes of vomiting or dry heaves or requires use of medication for vomiting or nausea at any time during the diary reporting period.

The subject/parent/caregiver will be told that he/she will be contacted daily on Days 2 to 5 and on Day 6, if the subject's post-treatment visit is not scheduled for that day, to remind him/her to record episodes of vomiting/dry heaves and use of medication for vomiting or nausea in the diary. Episodes of vomiting/dry heaves and use of medication for vomiting or nausea that occur on Day 6 (within the 120 hours) will be recorded on Day 5 of the Patient Diary. The subject/parent/caregiver will be instructed to return the completed diary at the Post-Treatment Visit.

7.1.1.10 Laboratory and ECG Safety Test Review

ECG and laboratory safety tests results, including urine pregnancy test (for females of reproductive potential), will be reviewed prior to randomization/treatment to confirm that the results are clinically acceptable and the subject meets the study requirements. If the subject's ECG, and blood and urine laboratory tests were not done within the preceding 7 days to the Randomization/Treatment Visit, they will be repeated. Any results found clinically unacceptable may be repeated.

It is advised that investigators consider correction of known electrolyte abnormalities prior to administration of ondansetron, consistent with ondansetron labeling and local standard of care.

Clinically significant findings from the screening laboratory safety tests and/or ECG should be recorded as medical history. For laboratory safety tests and/or ECG performed after treatment, any clinically significant changes should be recorded as AEs.

7.1.1.11 Rescue Medication Prescription

In Cycle 1, subjects will be provided with a prescription for rescue medication according to investigator preference. Permitted rescue medications are listed in Section 5.6 – Rescue Medications & Supportive Care. Subject/parent/caregiver will be instructed that the subject is allowed to take medication if needed for established nausea or vomiting, but should not take the medication to prevent nausea or vomiting. Subject/parent/caregiver will be instructed on how to record any medication taken for vomiting or nausea in the Patient Diary. See section 7.1.1.9 - Patient Diary Education for Subject/Parent/Caregiver.

In optional Cycles 2 to 6, the subject may be provided with a prescription for rescue medication according to investigator preference.

7.1.1.12 Subject/Parent/Caregiver Diary Completion - Cycle 1 Only

The subject/parent/caregiver will record the date and time of any episodes of vomiting/dry heaves and use of medication for vomiting or nausea in the Patient Diary. The diary will be completed on Days 1 to 6 (for 120 hours after initiation of first emetogenic chemotherapy).

7.1.1.13 Telephone or Direct Contact (scripted questions) - Cycle 1 Only

Site staff will contact (either telephone or in person) the subject/parent/caregiver on Days 2 to 5 and on Day 6, if the subject's post-treatment visit is not scheduled for that day, to remind him/her to record episodes of vomiting/dry heaves and use of medication for vomiting or nausea. All attempted and completed telephone contacts will be documented by the trial site.

The following questions, in the sequence listed, will be asked during each contact:

1. "Do you have your/your child's diary with you? If not, please obtain it and I will wait."

2. "Did you/your child have any episodes of vomiting/dry heaves in the last 24 hours?"

"If yes, how many times? At what time(s)? Did you record this in the diary? If not, please record it now."

If the subject has had episodes of vomiting or dry heaves they should be reminded that they still need to complete the diary.

If the subject did not have any episodes of vomiting or dry heaves in the preceding 24 hours, they should be reminded to check the diary box for that day indicating that they did not have any episodes of vomiting or dry heaves.

3. "Did you/your child need medication to treat vomiting or nausea?"

"If yes, how much? At what time(s)? Did you record this in the diary? If not, please record it now."

If the subject has taken medication for vomiting or nausea, they should be reminded that they still need to complete the diary.

If the subject has not taken any medication for vomiting or nausea in the preceding 24 hours, they should be reminded to check the diary box for that day indicating that they did not take any medication for vomiting or nausea.

At each contact, the subject/parent/caregiver will be reminded that they/their child can still take medication if they have vomiting or nausea.

At the Day 6 contact (or Day 5 contact if Post-Treatment Visit is on Day 6), subject/parent/caregiver should be reminded to bring the completed diary to the next visit.

The questions relating to episodes of vomiting or dry heaves, and medications for vomiting or nausea are designed ONLY to assist subject/parent/caregiver in the proper completion of the Patient Diary. The answers to questions about the endpoints of episodes of vomiting or dry heaves and medications for vomiting or nausea should NOT be recorded electronically by the person making the contact; rather the subject/parent/caregiver should be instructed to properly complete the diary.

During each contact, the subject/parent/caregiver will also be reminded to notify the investigator immediately of any adverse event.

7.1.1.14 Patient Diary Review/Collection (with Subject/Parent/Caregiver) - Cycle 1 Only

Subjects will return to the study site once during Day 6 to 9 and will bring the Patient Diary.

- The site staff will review the Patient Diary in detail, making sure that there are no errors, ambiguities, or missing data. All medications listed in the diary as medications for vomiting or nausea will be reviewed with the subject/parent/caregiver to confirm that they were actually taken to treat established nausea, vomiting, or both. If an error is found, the subject/parent/caregiver will be instructed to cross out the first answer with a single line and to put his/her initials and date next to the correct answer.

- The diary will be initialed and dated by the subject/parent/caregiver (including relationship to patient, if applicable), in the presence of the investigator or his/her delegate, as verification of a true record. The site staff will collect the diary.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Full Physical Examination - Cycle 1 Only

The investigator or qualified designee will perform a complete physical exam during the screening period according to local standard of care. A complete physical examination may include the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated.

Clinically significant abnormal findings should be recorded as medical history.

7.1.2.2 Directed Physical Examination

Physical examinations after the Screening Visit will be directed exams. The investigator or qualified designee will perform a symptom-focused exam as clinically indicated. New clinically significant abnormal findings found after receiving study therapy on Day 1 will be reported as adverse events. If a randomized subject is discontinued for any reason, every attempt should be made to perform a final directed physical examination if indicated.

7.1.2.3 Height - Cycle 1 only

Height will be obtained with the subject's shoes off.

7.1.2.4 Weight

Body weight will be obtained with the subject's shoes off and jacket or coat removed.

7.1.2.5 Vital Signs

The investigator or qualified designee will assess vital signs as indicated in Section 6.0 - Trial Flow Chart. Vital signs include blood pressure, heart rate, respiratory rate and axillary/oral/rectal/temporal/tympanic temperature. Blood pressure and heart-rate should be obtained with the subject in a seated, semi-recumbent, prone or supine position. An appropriately sized blood pressure cuff will be used. At the randomization/treatment visits, blood pressure and heart rate measurements will be taken prior to and ~15 minutes after fosaprepitant infusion, prior to chemotherapy infusion. Every effort should be made to collect these measurements using the same arm and body position.

7.1.2.6 12-Lead Electrocardiogram - Cycle 1 only

A screening 12-lead ECG will be obtained and read using local standard procedures. If the subject's ECG from the Screening Visit was not done within the preceding 7 days to the Randomization Visit, it will be repeated.

In those subjects with a baseline potassium and/or magnesium level below the normal range for the subject's age that were not corrected prior to randomization, another ECG will be obtained ~2 (no later than 3) hours after initial administration of ondansetron.

7.1.2.7 Lansky or Karnofsky Performance Status Evaluation - Cycle 1 only

The Lansky and Karnofsky Performance Status Scales (see Section 12.4 - Lansky and Karnofsky Performance Status Scales) will be used to evaluate if the subject meets the study inclusion criterion. The Lansky Play-Performance Scale will be used to evaluate subjects ≤16 years of age. The Karnofsky Performance Scale will be used to evaluate subjects >16 years of age. Subjects must have a score ≥ 60 to participate in this study (see Section 5.1.2– Subject Inclusion Criteria).

7.1.2.8 Fosaprepitant or Matching Placebo for Fosaprepitant Administration

Fosaprepitant or matching placebo dose is initiated at ~90 minutes prior to initiation of the first emetogenic chemotherapy and administered via a central venous catheter over a period of ~60 minutes for subjects <12 years old and ~60 minutes prior to initiation of the first emetogenic chemotherapy and administered via a central venous catheter over a period of ~30 minutes for subjects 12 to 17 years old. The infusion will be complete ~30 minutes prior to chemotherapy initiation.

7.1.2.9 IV Ondansetron Administration - Cycle 1 only

IV ondansetron is required for Cycle 1 and will be supplied for prophylaxis use only by the Sponsor to be used on days of chemotherapy administration and up to 24 hours after chemotherapy. For subjects 6 months to 17 years old, the first dose on Day 1 will be administered no later than 30 minutes prior to initiation of the first emetogenic chemotherapy. The timing of the first dose of ondansetron administration for subjects <6 months old should be scheduled according to local standard of care. Additional doses of IV ondansetron on Day 1 will be administered according to local standard of care. For multi-dose chemotherapy regimens, IV ondansetron can be administered on subsequent days if clinically warranted and per local standard of care; however, it should only be administered on the day(s) of chemotherapy administration and up to 24 hours after chemotherapy administration.

7.1.2.10 5-HT_3 Antagonist Administration - Optional Cycles 2-6

For optional Cycles 2 to 6, any commercially available 5-HT_3 antagonist may be used as part of the antiemetic regimen and will be supplied locally by the study site. The 5-HT_3 antagonist will be administered per product label or local standard of care with the first dose administered prior to initiation of chemotherapy.

7.1.2.11 Optional Dexamethasone Administration

Dexamethasone may be administered as part of an anti-emetic regimen based on local standard of care, but no later than 30 minutes prior to initiation of the first emetogenic

chemotherapy. For subjects receiving fosaprepitant, the dose of dexamethasone should be reduced to 50% of the prescribed dose when administered within 48 hours following administration of fosaprepitant. Dose reduction applies to dexamethasone used prophylactically and as rescue medication. No dose adjustment will be made for subjects receiving placebo for fosaprepitant.

In Cycle 1, for multi-dose chemotherapy regimens, IV dexamethasone can be administered on subsequent days if clinically warranted and per local standard of care; however, it should only be administered on the day(s) of chemotherapy administration and up to 24 hours after chemotherapy administration.

7.1.2.12 Chemotherapy Infusion

Subjects will receive at least one chemotherapeutic agent associated with moderate or high risk of emetogenicity for a documented malignancy, or a chemotherapy regimen not previously tolerated due to vomiting. See Section 12.5, Emetogenicity of Commonly Used Chemotherapeutic Agents, for guidance on the classification of chemotherapy agents.

The chemotherapy regimen will be infused per the local standard of care. The date and time of initiation of the first emetogenic chemotherapy infusion will be designated as T_{zero} (0 hour) for the cycle. In Cycle 1, this date and time will be recorded by the site staff on the front page of the Patient Diary.

The dose, start and stop date/time for all chemotherapy agents will be recorded.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be drawn over the course of the trial, including approximate blood volumes drawn by visit and by sample type per subject can be found in Section 12.6 – Approximate Blood Volumes Drawn by Trial Visit and by Sample Types.

7.1.3.1 Local Laboratory Safety Evaluations (Hematology, Chemistry)

Laboratory tests for hematology and chemistry are specified in Table 5.

Table 5 Laboratory Tests

Hematology	**Chemistry** (*serum/plasma*)	**Other**
Hematocrit	Albumin	Urine Pregnancy Test - females of childbearing potential
Hemoglobin	Alkaline phosphatase	Serum Pregnancy Test, if per local standard of care or if indicated
Platelet count	Alanine aminotransferase (ALT)	
White Blood Cell (WBC) total and differential	Aspartate aminotransferase (AST)	
	Bicarbonate	
	Calcium, Total	
	Calcium, Ionized* (whole blood, plasma or serum)	
	Chloride	
	Creatinine	
	Glucose	
	Magnesium	
	Potassium	
	Sodium	
	Total Bilirubin	
	Urea/Blood Urea Nitrogen	

* At selected sites, blood samples for ionized calcium will be drawn in Cycle 1 only at the screening visit and at the randomization visit ~ 15 minutes after completion of fosaprepitant/placebo infusion, prior to the start of chemotherapy. Ionized calcium will not be drawn at any other time points.

Laboratory safety evaluations and Urine Pregnancy Test will be performed by the local laboratory according to local procedures and results will be documented on the subject's chart. Pre-dose testing that are conducted more than 7 days prior to dosing will be repeated and reviewed prior to fosaprepitant dosing in a cycle.

If a female subject reaches menarche (menstruates for the first time), a urine pregnancy test must be performed. Results must be obtained prior to study drug administration. Urine pregnancy testing should be repeated at subsequent visits if the subject reports non-compliance to birth control methods, if there is a question about potential pregnancy or as

required by local guidelines. **Note:** a serum pregnancy test can be performed instead of the urine test per local regulatory requirements or standard of care.

7.1.3.2 Pharmacokinetic (PK) Evaluations (Cycle 2 Only)

PK samples for aprepitant will be collected from all subjects participating in optional Cycle 2 at two time points: Day 1, end of fosaprepitant infusion and approximately 2 to 4 hours after (completion) of fosaprepitant infusion.

If the subject is still at the site or is returning to the site on Cycle 2 Day 2 or 3 (e.g., to receive additional chemotherapy), PK sample(s) will be collected at up to two additional time points: Cycle 2, Day 2 (ideally ~23 to 25 hours after fosaprepitant infusion on Cycle 2, Day 1); and Cycle 2, Day 3 (ideally ~46 to 50 hours after fosaprepitant infusion on Cycle 2, Day 1). Subjects who will not be at the site on Cycle 2, Days 2 and 3 do not need to return for PK sampling.

Subjects who have a multi-lumen central venous catheter will have one line designated strictly for the infusion of fosaprepitant and another line designated for the collection of PK. To avoid the potential of cross contamination, a subject that has fosaprepitant administered through a single lumen central venous catheter cannot have PK samples drawn from that same line on the day of fosaprepitant administration. To obtain PK samples on the day of fosaprepitant administration, a peripheral line should be inserted to perform blood draws at the specified time points. A single lumen catheter can be used to draw PK samples on Cycle 2, Day 2 and Cycle 2, Day 3. Venipuncture may be performed when clinically indicated.

Sample collection, storage and shipment instructions for the PK samples will be provided in the operations/laboratory manual.

7.1.3.3 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Buccal swab for future biomedical research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Follow-Up/Discontinuation visit for the applicable cycle should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who discontinue will be instructed to come in for a Discontinuation Visit within 72 hours and

complete all discontinuation procedures. See the required procedures for the Follow-Up/Discontinuation Visit in Section 6.0 - Trial Flow Chart. If the subject discontinues from Cycle 1 prior to the Post Treatment Visit, the subject/parent/caregiver will be asked if the subject experienced any episodes of vomiting/dry heaves since the previous visit/phone contact and if medication was taken to treat established nausea and/or vomiting. The subject/parent/caregiver will be asked to update the diary with the information, if not already recorded. In addition, the site staff will review the Patient Diary in detail with the subject/parent/caregiver as detailed in Section 7.1.1.14 – Patient Diary Review/Collection (with Subject/Parent/Caregiver).

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subject/parent/legal guardian may withdraw consent and/or assent (if applicable) for Future Biomedical Research and have their specimens and all derivatives destroyed. Subject/parent/legal guardian may withdraw consent and/or assent (if applicable) at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox PPD and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the toxicity grade of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call

center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory/ECG equipment – as required for inclusion labs and trial assessments

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Cycle 1

7.1.5.1.1 Screening (Visit 1)

Up to 28 days prior to randomization, a potential subject will be evaluated to determine that he/she fulfills the entry requirements as set forth in Section 5.1, Entry Criteria. The Screening Visit can occur the same day as the Randomization Visit (Day 1), as long as all required trial procedures for both visits are completed/reviewed prior to study drug administration and subject eligibility is confirmed.

Written consent and assent (if applicable) must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject/parent/guardian signing consent/assent that are part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame and the consent form indicates that such test results may be used.

Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory Safety (including ionized calcium at selected sites), Urine Pregnancy and ECG testing must be completed within 7 days prior to initiation of study medication.

A subject may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of repeating a screening test if performed within the specified time frame and the results meet the inclusion/exclusion criteria.

If a subject/parent/legal guardian has signed an informed consent/assent but the subject is not randomized into the study, the investigator will collect information at the Screening visit, including: basic demographics, inclusion/exclusion criteria, subject disposition, laboratory data and adverse event information, as applicable. Unless otherwise directed, no other data need to be collected for these subjects.

7.1.5.1.2 Randomization (Visit 2)

The subject will be required to return to the study site approximately 2.5 hours prior to initiation of emetogenic chemotherapy in order to allow adequate time to perform all study required procedures.

The subject/parent/caregiver will be asked by the site staff: "Did you (or your child) have any episodes of vomiting or dry heaves in the last 24 hours?" Any subject who has vomited within the 24 hours prior to the scheduled start of emetogenic chemotherapy will not be permitted to participate in the study on that day. The subject may be re-evaluated for study participation on a subsequent day if initiation of emetogenic chemotherapy is also delayed. If chemotherapy is not delayed, subject may be re-evaluated at a subsequent cycle.

The subject/parent/caregiver will be asked if the subject has had any changes in their health or taken any medications since the previous visit and the information will be recorded. The subject must continue to fulfill the inclusion and exclusion criteria in order to be randomized.

Preliminary screening laboratory test results will be reviewed. If the subject's screening laboratory tests and ECG were obtained within the preceding 7 days, they will only need to be repeated if the subject's clinical status has changed. If the screening laboratory tests and ECG were completed >7 days prior to Day 1, then they will be repeated.

Prior to the initiation of the first emetogenic chemotherapy, the subject/parent/caregiver will be given a Patient Diary and will be educated on the appropriate completion of the diary.

At selected sites, a blood sample for ionized calcium will be collected ~15 minutes after completion of fosaprepitant/placebo infusion, prior to the start of chemotherapy.

7.1.5.1.3 Telephone/Direct Contact Visits

The site staff will contact the subject/parent/caregiver daily on Days 2 to 5 and on Day 6, if the subject's post-treatment visit is not scheduled for that day, to ensure the diary is being completed. Telephone or direct contact will be made based on subject location. See Section

7.1.1.13, Telephone or Direct Contact (scripted questions) for details on questions to ask during each contact.

Note: Site staff must make every effort to make contact with the subject/parent/caregiver on all diary days (including weekends) in order to ensure compliance with diary completion. All attempted and completed telephone contacts will be documented by the trial site.

The subject/parent/caregiver will be reminded to bring the Patient Diary to the next visit.

7.1.5.1.4 Post-Treatment (Visit 3)

The subject will be required to return to the study site with the Patient Diary once during study Day 6 to 9 after the diary reporting period has been completed. The diary will be reviewed with the subject as defined in Section 7.1.1.14 - Patient Diary Review/Collection (with Subject/Parent/Caregiver).

7.1.5.1.5 Follow-Up/Discontinuation (Visit 4)

The subject will be required to return to the study site once during study Day 15 to 20 (14 to 19 days following Treatment Day 1). For subjects who elect to participate in Optional Cycle 2, this visit can be scheduled to coincide with the start of the next chemotherapy cycle provided that the next round of chemotherapy is 14 to 19 days after Treatment Day 1.

If there has been an interval hospitalization, only the discharge medications will be recorded.

If a subject does not elect to participate in the Optional Cycles 2 to 6, a discontinuation visit will be registered in IVRS/IWRS and reasonable effort should be made to collect the subject identification card.

7.1.5.2 Optional Cycles 2 to 6

A subject who completes Cycle 1 may be invited to participate in optional Cycles 2 to 6. A subject may participate in a total of 5 optional cycles. Each subject will be allowed a maximum of 6 months from the end of Cycle 1 to complete the optional cycles.

A minimum of 14 days is required between Day 1 in a cycle and Day 1 in a subsequent cycle.

7.1.5.2.1 Treatment Visit

Parent/legal guardian of subjects < 18 years old or subjects 18 years of age participating in the optional cycles must provide documented consent prior to the start of Cycle 2. Written assent from subjects 12 to 17 years of age, or as required per local institutional guidelines, will also be collected.

After all required study procedures have been completed and subject's eligibility has been confirmed, the treatment visit will be registered in IVRS/IWRS for study drug component ID assignment.

The subject will receive open-label fosaprepitant. Any commercially available 5-HT_3 antagonist may be used as part of the antiemetic regimen with or without dexamethasone. Subjects may be provided with a prescription for rescue medication according to investigator preference.

In Cycle 2 only, PK samples for aprepitant will be collected as described in Section 7.1.3.2 - Pharmacokinetic (PK) Evaluations.

7.1.5.2.2 Follow-Up/Discontinuation Visit

The subject will be required to return to the study site once during study Day 15 to 20 (14 to 19 days following Treatment Day 1) of an optional cycle. For subjects who elect to participate in the next optional cycle, this visit can be scheduled to coincide with the start of the next chemotherapy cycle provided that the next round of chemotherapy is 14 to 19 days after Treatment Day 1 of the current cycle.

If there has been an interval hospitalization, only the discharge medications will be recorded.

If a subject does not elect to participate in any additional optional cycles, a discontinuation visit will be registered in IVRS/IWRS. A subject who has completed the 5 optional cycles will have completed the study. Reasonable effort should be made to collect the subject identification card when a subject discontinues from or completes the trial.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

In Cycle 1, from the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. Events related to vomiting and dry heaves/retching are not defined as adverse events during the diary reporting period (120 hours following chemotherapy infusion) unless they meet the definition of a serious adverse event as described in Section 7.2.3.1 – Serious Adverse Events. Beyond this period, vomiting and dry heaves/retching will be considered as adverse events.

In Cycles 2 to 6, all serious adverse event(s), non-serious drug-related adverse event(s), and adverse event(s) leading to discontinuation from the study will be recorded. This includes the time period from the completion of Cycle 1 through 14 days following treatment in the last optional cycle and at each examination.

The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is defined as a single dose of study medication that exceeds the prescribed dose for each age range.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the

upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 6 and according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

The NCI Common Terminology for Adverse Events (CTCAE), version 4.0 will be used to grade all adverse events. The criteria will be provided in the Investigator Trial File Binder (or equivalent) and can be accessed electronically on the following website: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Table 6 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Efficacy Analyses

The primary and secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 7 below.

The primary hypothesis will be evaluated by comparing the fosaprepitant regimen to the control regimen with respect to the proportion of subjects reporting Complete Response in the delayed phase (>24 to 120 hours) following initiation of emetogenic chemotherapy in Cycle 1.

The three secondary hypotheses will be evaluated by comparing the fosaprepitant regimen to the control regimen with respect to the proportion of subjects reporting Complete Response in the acute phase (0 to 24 hours), in the overall phase (0 to 120 hours) and No Vomiting in the overall phase (0 to 120 hours).

The multiplicity strategy described in Section 8.2.6 will be used to control Type I error rate when testing the primary and 3 secondary hypotheses.

Table 7 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Objective				
Proportion of subjects with complete response from >24 to 120 hours following initiation of emetogenic chemotherapy	P	CMH exact test ‡	ITT	Missing is treated as failure
Secondary Objectives				
Proportion of subjects with complete response from 0 to 24 hours following initiation of emetogenic chemotherapy	P	CMH exact test	ITT	Missing is treated as failure
Proportion of subjects with complete response from 0 to 120 hours following initiation of emetogenic chemotherapy	P	CMH exact test	ITT	Missing is treated as failure
Proportion of subjects with no vomiting from 0 to 120 hours following initiation of emetogenic chemotherapy	P	CMH exact test	ITT	Missing is treated as failure

† P=Primary approach.
‡ Stratified by age (<2 years, 2 to 17 years), receipt of High Risk emetogenic chemotherapy agent in Cycle 1 (yes, no) and use of dexamethasone as an antiemetic in Cycle 1 (yes, no); CMH = .Cochran-Mantel-Haenszel

8.1.2 Safety Analysis

The All-Subjects-as-Treated (ASaT) population will be employed for safety analyses.

For this study, there are no pre-specified events of interest, i.e., no Tier-1 events.

8.1.3 Power and Sample Size

The study intends to enroll approximately 180 subjects with 1:1 randomization to the fosaprepitant regimen and the control regimen, to achieve 80% power (1-sided, α=0.025) to demonstrate the primary hypothesis that the fosaprepitant regimen is superior to the control regimen as measured by the proportion of subjects with Complete Response from >24 to 120 hours following initiation of emetogenic chemotherapy. This is based on the assumption of an underlying treatment difference of 20% across all age groups. We assume that the response rate for the control regimen will be approximately 25% (similar to the observed response rate for Complete Response Delayed in the oral study Protocol 208) and the response rate for the fosaprepitant regimen is 45%.

If PK/PD data from the ongoing Protocol 029 do not support opening enrollment for one or more age group(s), the sample size and underlying treatment difference assumption may be adjusted, but the overall power of the study will be maintained.

8.2 Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

8.2.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

Cycle 1 of this study will be conducted as a double-blind study under in-house blinding procedures. Additional chemotherapy cycles will be conducted as a fosaprepitant open-label study. The official, final database for Cycle 1 will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete. Results from additional cycles of chemotherapy will be presented along with those of Cycle 1 in the CSR.

The Clinical Biostatistics department will generate the randomization schedule(s) for study treatment assignment. Randomization will be implemented using an interactive voice response system / integrated web response system (IVRS/IWRS).

8.2.2 Hypotheses

Objectives and hypotheses of the study are stated in Section 3.0. The null hypothesis is that the fosaprepitant regimen is not superior to the control regimen.

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints. Efficacy data will not be collected during Cycles 2 to 6. PK data will be evaluated in Cycle 2 only and safety data will be evaluated in all cycles.

8.2.3.1 Efficacy Endpoints

The primary efficacy endpoint will be the proportion of subjects with Complete Response in the >24 to 120 hours following initiation of emetogenic chemotherapy.

The secondary efficacy endpoints will be: the proportion of subjects with Complete Response in the 0 to 24 hours following initiation of emetogenic chemotherapy; the proportion of subjects with Complete Response in the 0 to 120 hours following initiation of emetogenic

chemotherapy; and the proportion of subjects with No Vomiting, irrespective of use of rescue medication, in the 120 hours following initiation of emetogenic chemotherapy.

In addition to the above mentioned efficacy endpoints, the exploratory endpoints of the number of emetic episodes, the number of subjects with no use of rescue medication, the time to first rescue medication, and the time to first vomiting in the 120 hours following initiation of emetogenic chemotherapy, and the Complete Response using an alternative definition of "acute" and "delayed" phases will be assessed and presented.

8.2.3.2 Safety Endpoints

There are no pre-specified events of interest for this study (i.e. no Tier 1 events).

Safety endpoints that will be assessed include clinical and laboratory adverse events that are considered drug-related, serious, serious drug-related, or lead to discontinuation from the study.

8.2.3.3 Pharmacokinetic Endpoints

The sparse PK samples may be used to calculate the PK endpoints for aprepitant (e.g. AUC0-∞, AUC0-24, Cmax, Tmax, t1/2, CL/F, C24hr, and C48hr).

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Intent-to-Treat (ITT) population which consists of all subjects (in the group they were) randomized and who received any study drug will serve as the primary population for the analysis of efficacy data in this study. A supportive analysis will be performed for the primary efficacy endpoint using the Full Analysis Set (FAS) population. The FAS population is a subset of all randomized subjects including all subjects who have received chemotherapy, received a dose of study drug and have at least one post-treatment efficacy assessment. Subjects excluded from the FAS will be considered as having an unfavorable response in the ITT analysis.

An additional supportive analysis using the Per-Protocol (PP) population will be performed for the primary efficacy endpoint. The Per-Protocol population excludes subjects due to important deviations from the protocol that may substantially affect the result of the primary efficacy endpoint. The final determination on protocol violations/deviations, and thereby the composition of the Per-Protocol population, will be made prior to the final unblinding of the database and will be documented in a separate memo and/or listing.

Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods.

8.2.4.2 Safety Analysis Populations

The All subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of any study drug. Subjects will be included in the treatment group corresponding to the study drug they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study drug for the entire treatment period will be included in the treatment group corresponding to the study drug actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study drug is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.2.5 Statistical Methods.

8.2.4.3 Pharmacokinetic Analysis Populations

The Per-Protocol population for PK will be those who participate in optional Cycle 2. The Per-Protocol population for PK excludes subjects or specific PK samples from a subject due to important deviations from the protocol that may substantially affect the results of the PK endpoint.

8.2.5 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 8.2.5.2, Statistical Methods for Safety Analyses. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.6 Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

8.2.5.1 Statistical Methods for Efficacy Analyses

The primary efficacy analysis will compare the fosaprepitant regimen to the control regimen with respect to the proportion of subjects reporting Complete Response in the delayed phase (>24 to 120 hours) following initiation of emetogenic chemotherapy.

The secondary efficacy analyses will compare the fosaprepitant regimen to the control regimen with respect to the proportion of subjects reporting Complete Response (acute and overall) and the proportion of subjects reporting No Vomiting overall.

The treatment comparisons for Complete Response and No Vomiting will be made using the CMH Exact test with 3 strata defined as age (<2 years, 2 to 17 years), receipt of High Risk emetogenic chemotherapy agent in Cycle 1 (yes, no), and use of dexamethasone as an

antiemetic in Cycle 1 (yes, no). The superiority hypotheses will be evaluated by comparing the 1-tailed p-value to 0.025 and significance declared if this p-value is ≤0.025.

A supportive analysis will be made using a logistic regression model that includes terms for treatment (fosaprepitant regimen, control regimen), age (<2 years, 2 to 17 years), receipt of a High Risk emetogenic chemotherapy agent in Cycle 1 (yes, no) and use of dexamethasone as an antiemetic in Cycle 1 (yes, no).

The age category (<2 years, 2 to 17 years) in the analysis models may be adjusted if PK/PD data from the ongoing Protocol 029 do not support opening enrollment for one or more age group(s).

Any vomiting or use of rescue therapy within a phase will define a subject as having an unfavorable response for that phase for all 3 efficacy subject populations (ITT, FAS and PP). Subjects with missing binary data for the primary and secondary endpoints will be classified as non-responder/failure in both the ITT and FAS efficacy analyses. In the PP population, any missing data will exclude the subject from the analysis within a phase.

For the exploratory analysis of time to first use of rescue medication, Kaplan-Meier curves depicting the percentage of subjects who did not use rescue medication, since the initiation of emetogenic chemotherapy, will be presented. For the time to first vomiting analysis, Kaplan-Meier curves depicting the percentage of subjects who are vomiting-free, ignoring rescue, since the initiation of emetogenic chemotherapy will also be presented. The Log-Rank test will be used for the treatment comparison. Descriptive summary will be made for number of episodes and number of subjects with no use of rescue medication in the overall phase. Number and proportion of subjects with Complete Response using alternative definition of "acute" and "delayed" phase will be summarized. The alternative acute phase will be defined as the period from initiation of the first dose of emetogenic chemotherapy until 24 hours post-initiation of the last dose of emetogenic chemotherapy. The alternative delayed phase will be defined as the period from the end of the acute phase to 120 hours post-initiation of the first dose of emetogenic chemotherapy on day 1. Because of the expected variability in the number of days of emetogenic chemotherapy among subjects, the length of the alternative acute and delayed phases is also expected to vary. Therefore, to minimize this variability during the analyses, these alternative phases may also be evaluated using subgroups based on days of emetogenic chemotherapy.

Table 8 summarizes the key efficacy analyses.

Table 8 Summary of Analysis Strategy for Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach
Primary Objectives				
Proportion of subjects with complete response from >24 to 120 hours following initiation of emetogenic chemotherapy	P	CMH exact test [‡]	ITT	Missing is treated as failure
Proportion of subjects with complete response from >24 to 120 hours following initiation of emetogenic chemotherapy	S	CMH exact test	FAS	Missing is treated as failure
Proportion of subjects with complete response from >24 to 120 hours following initiation of emetogenic chemotherapy	S	CMH exact test	PP	Excluded in the analysis
Proportion of subjects with complete response from >24 to 120 hours following initiation of emetogenic chemotherapy	S	Logistic Regression Model	ITT	Missing is treated as failure
Secondary Objectives				
Proportion of subjects with complete response from 0 to 24 hours following initiation of emetogenic chemotherapy	P	CMH exact test	ITT	Missing is treated as failure
Proportion of subjects with complete response from 0 to 24 hours following initiation of emetogenic chemotherapy	S	Logistic Regression Model	ITT	Missing is treated as failure
Proportion of subjects with complete response from 0 to 120 hours following initiation of emetogenic chemotherapy	P	CMH exact test	ITT	Missing is treated as failure
Proportion of subjects with complete response from 0 to 120 hours following initiation of emetogenic chemotherapy	S	Logistic Regression Model	ITT	Missing is treated as failure
Proportion of subjects with no vomiting from 0 to 120 hours following initiation of emetogenic chemotherapy	P	CMH exact test	ITT	Missing is treated as failure
Proportion of subjects with no vomiting from 0 to 120 hours following initiation of emetogenic chemotherapy	S	Logistic Regression Model	ITT	Missing is treated as failure

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Exploratory Objective				
Time to first use of rescue medication	P	Kaplan-Meier curve and Log-Rank test	ITT	None
Time to first vomiting in 120 hours	P	Kaplan-Meier curve and Log-Rank test	ITT	None
Number of emetic episodes in 120 hours	P	Descriptive Summary	ITT	Observed data
Number of subjects with no use of rescue medication in 120 hours	P	Descriptive Summary	ITT	Missing is treated as failure
Proportion of subjects with complete response using the alternative definition of "acute" and "delayed" phase.	S	Descriptive Summary	ITT	Missing is treated as failure

† P=Primary approach; S=Secondary approach.
‡ Stratified by age (<2 years, 2 to 17 years), receipt of High Risk emetogenic chemotherapy agent in Cycle 1 (yes, no) and use of dexamethasone as an antiemetic in Cycle 1 (yes, no); CMH = Cochran-Mantel-Haenszel

The strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple efficacy endpoints, and/or multiple time points is described in Section 8.2.6, Multiplicity.

8.2.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, vital signs, and ECG measurements.

Cycle 1

The analysis of safety results will follow a tiered approach (Table 9). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. This protocol does not have a Tier 1 analysis. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse events (specific terms as well as system organ class terms) that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse events and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, summary statistics for the difference between treatment groups will also be provided, along with nominal p-values for between-group differences.

For this protocol, there are no prespecified events of interest (i.e. no Tier 1 events). The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. Ninety-five percent (95%) confidence intervals (Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method [22], an unconditional, asymptotic method.

Table 9 Analysis Strategy for Key Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	None	--	--	--
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Discontinuation due to a Drug-Related AE		X	X
	Specific AEs, SOCs‡ (incidence ≥4 in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs‡ (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

† Adverse Experience references refer to both Clinical and Laboratory AEs.
‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
NOTE: SOC= System Organ Class; X = results will be provided.

Optional Cycles 2 to 6

For cycles 2 to 6, proportions will be displayed for serious adverse event(s), drug-related adverse event(s), and adverse event(s) leading to discontinuation from the study, which occur during the fosaprepitant treatment period plus 14 days post therapy.

8.2.5.3 Statistical Methods for Pharmacokinetics

Population pharmacokinetic methods will be used to analyze the sparse plasma concentration results. Data from previous available CINV (MK-0869 Protocols 097 and 134; MK-0517-029) and PONV (MK-0869 Protocol 148) pharmacokinetic studies conducted in pediatric subjects from birth to 17 years old will be evaluated for inclusion in the population modeling to further characterize the pharmacokinetic profile in pediatric subjects and support modeling the sparse data. Briefly, NONMEM software will be used to develop a population pharmacokinetic model that describes the plasma concentration-time data, with appropriate covariates such as body size and age included in the modeling. Model development will be guided by selection of models with parsimonious structure. This population model will be used to estimate the pharmacokinetic parameters of aprepitant (e.g., AUC0-∞, AUC0-24, C_{max}, T_{max}, t1/2, CL/F, C24hr, and C48hr) for pediatric subjects following administration of fosaprepitant.

8.2.5.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reasons for discontinuation will be displayed. Demographic variables (e.g., age) baseline characteristics, primary diagnosis, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.2.6 Multiplicity

The following multiplicity strategy will be used to control Type I error in testing the primary and 3 secondary hypotheses.

First, the primary hypothesis will be tested at alpha = 0.025, 1-tailed. If the testing on the primary hypothesis is significant, then Hochberg method will be used to test all 3 secondary hypotheses at total alpha = 0.025, 1-tailed.

To be more specific, for the three secondary null hypotheses, the following procedures will be taken if the primary hypothesis is significant:

1. The maximum of the three p-values (one-sided) is compared with 0.025. If it is less than 0.025 (1-sided), then all three null hypotheses are rejected and claim the statistical significance for all three endpoints.

2. If the maximum of the three p-values is greater than 0.025, the null hypothesis associated with that p-value cannot be rejected (i.e. statistical significance cannot be claim for the corresponding endpoint). The next largest p-value will then be compared with alpha level of 0.025/2. If it is less than 0.025/2, the remaining two null hypotheses are rejected.

3. If the next largest p-value is greater than 0.025/2, the null hypothesis associated with this p-value cannot be rejected either. The smallest of the three p-values is then compared with alpha level of 0.025/3. If it is less than 0.025/3, the null hypothesis associated with this p-value is rejected. If it is greater than 0.025/3, the null hypothesis associated with this p-value cannot be rejected. In this case, all three null hypotheses cannot be rejected.

8.2.7 Sample Size and Power Calculations

This study will randomize approximately 180 subjects with approximately 90 subjects into the fosaprepitant regimen group and 90 subjects into the control regimen group and has 80% power to demonstrate the superiority of the fosaprepitant regimen over the control regimen at an overall one-sided, 2.5% alpha-level, if the underlying treatment difference in Complete Response is 20%. The power and sample size are based on the assumption of an underlying response rate of 25% for the control regimen (similar to the observed response rate for Complete Response Delayed in the oral aprepitant study Protocol 208) and of 45% for the fosaprepitant regimen. The Complete Response calculation is based on an asymptotic method proposed by Farrington and Manning [23] with 90 subjects in the active control arm and 90 subjects in the fosaprepitant regimen arm expected to be included in the analysis and is carried out using SAS v9.1. The minimum criterion for success is that the one-sided p-value < 0.025.

8.2.8 Subgroup Analyses and Effect of Baseline Factors

To explore whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated within each category of the following classification variables:

- Age category (birth to <2 years, 2 to <6 years, 6 to <12 years, and 12 to17 years). The category may be adjusted if PK/PD data from the ongoing Protocol 029 do not support opening enrollment for one or more age group(s).
- Sex (Female, Male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Multiple, Native Hawaiian or Other Pacific Island and White)
- Receipt of a High Risk emetogenic chemotherapy agent in Cycle 1 (Yes, No)
- Use of Dexamethasone as an antiemetic in Cycle 1 (Yes, No)
- Single versus multiple day chemotherapy

In addition, a summary of count and percentage of all adverse events will be provided for each age category listed above.

8.2.9 Interim Analysis

No interim analyses are planned for this study.

8.2.10 Compliance (Medication Adherence)

Study medication will be administered in a supervised clinical setting and missed or incorrect dosing will be uncommon. Subjects who miss a dose or take an incorrect dose will be described in the CSR as to why the dose was missed or incorrect.

8.2.11 Extent of Exposure

The extent of exposure (dose and duration) to fosaprepitant will be summarized by the number of subjects exposed to fosaprepitant for defined periods of time. In addition, the extent of exposure to ondansetron and dexamethasone will be summarized.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 10

Table 10 Product Descriptions

Product Name & Potency	Dosage Form
Fosaprepitant dimeglumine 150 mg	Lyophilized powder for injection
Ondansetron hydrochloride 2 mg/ml*	Solution for injection
*If ondansetron 2mg/ml supplies are not available, other formulations may be provided.	

All other supplies not indicated in Table 10 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number.

The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

For Cycle 1, the study site will receive open-label vials of fosaprepitant dimeglumine 150 mg. Ondansetron hydrochloride 2 mg/ml ampoules or vials will be received as open-label single units. The study site will supply its own source of normal saline (0.9% sodium chloride) to prepare the study drug and to be utilized as needed for blinding purposes to match fosaprepitant dimeglumine.

For the optional Cycles 2 to 6, open-label fosaprepitant dimeglumine will be packaged and supplied identical to Cycle 1. The 5-HT_3 antagonist will be sourced by the study site.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the randomization schedule for the trial to unblind subjects and to unmask treatment identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed and returned and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent/assent form, the subject/parent/legal guardian agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a

Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data,

correspondence with regulatory authorities and IRBs/ERCs, consent and assent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate

enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on

OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent/assent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent/assent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent/assent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent/assent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.2

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.2

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The buccal specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The buccal specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent and/or Assent (if applicable)

Informed consent/assent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent/assent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent/assent at next possible Subject Visit. Informed consent/assent must be obtained prior to collection of all Future Biomedical Research specimens. Consent/assent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the

consent/assent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent/assent will not have the specimen collected nor will they be discontinued from the main trial.

A template of each trial site's approved informed consent/assent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Buccal swab specimens for DNA isolation will be obtained at a time when the subject is having other trial procedures conducted. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

Subject/parent/legal guardian may withdraw consent and/or assent (if applicable) for Future Biomedical Research and have their specimens and all derivatives destroyed. Subject/parent/legal guardian may withdraw consent and/or assent (if applicable) at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox PPD and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These

data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Buccal swab specimens will be collected inside the cheek with no associated venipuncture to obtain the specimen. Therefore, there will not be an additional risk for the subject.

Merck has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all

specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

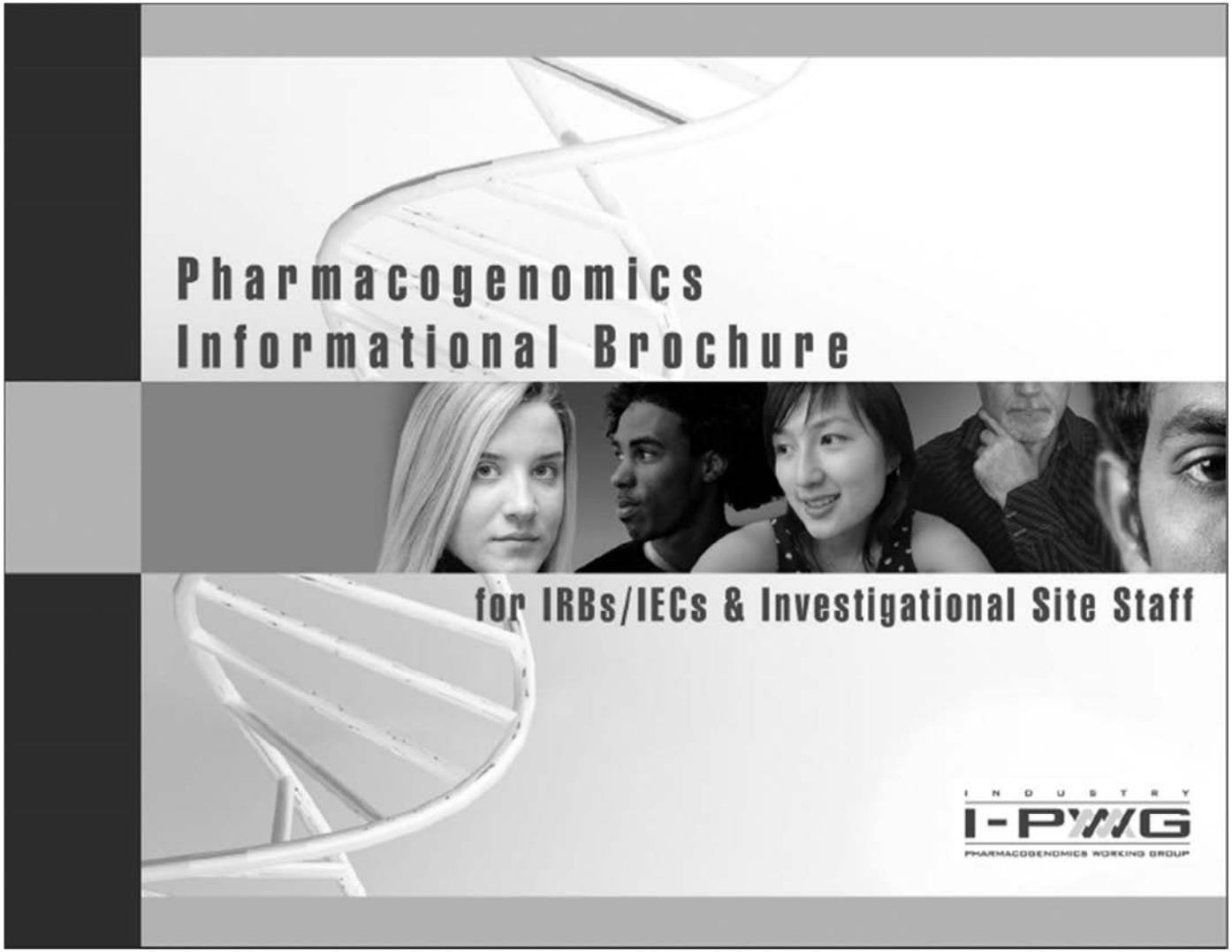
13. Questions

Any questions related to the future biomedical research should be e-mailed directly to PPD

14. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Pharmacogenomics Informational Brochure for IRBs/IECs & Investigational Site Staff



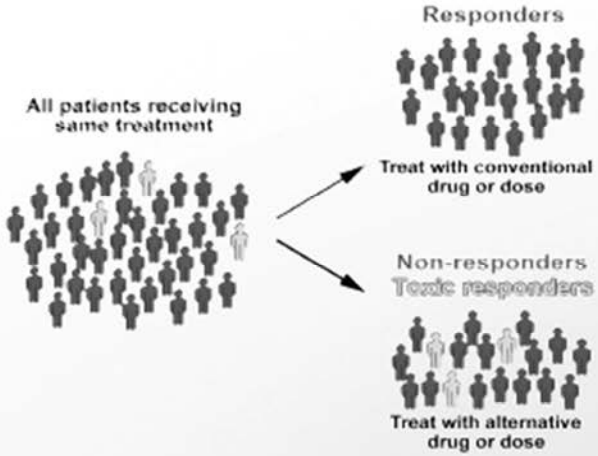
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid** (**DNA**). DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

I-PWG

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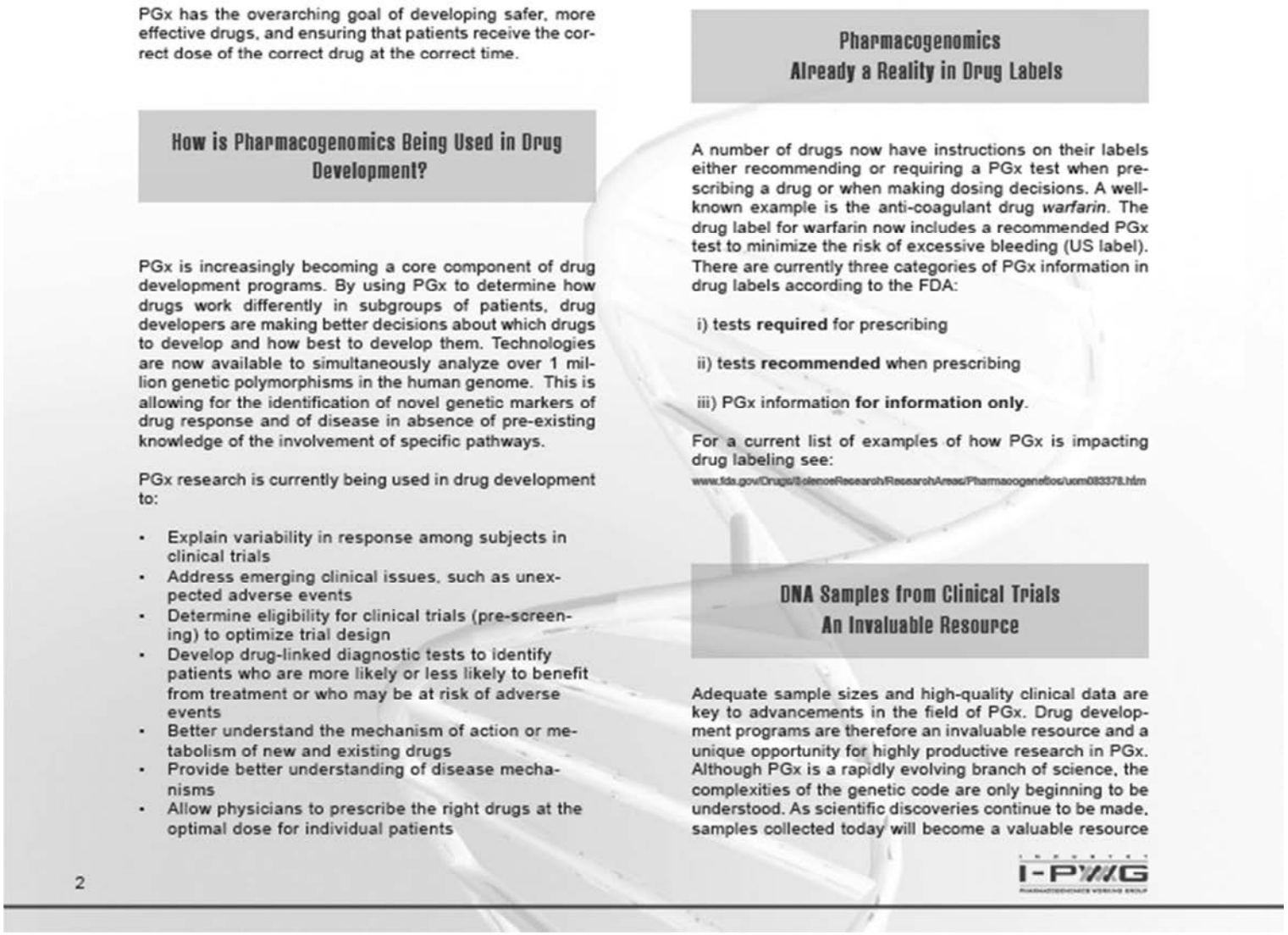
PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.
How is Pharmacogenomics Being Used in Drug Development?
PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.
PGx research is currently being used in drug development to:
• Explain variability in response among subjects in clinical trials
• Address emerging clinical issues, such as unexpected adverse events
• Determine eligibility for clinical trials (pre-screening) to optimize trial design
• Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
• Better understand the mechanism of action or metabolism of new and existing drugs
• Provide better understanding of disease mechanisms
• Allow physicians to prescribe the right drugs at the optimal dose for individual patients
2
Pharmacogenomics
Already a Reality in Drug Labels
A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug warfarin. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:
i) tests required for prescribing
ii) tests recommended when prescribing
iii) PGx information for information only.
For a current list of examples of how PGx is impacting drug labeling see:
www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
DNA Samples from Clinical Trials
An Invaluable Resource
Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource
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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

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http://www.i-pwg.org

12.4 Lansky and Karnofsky Performance Status Scales

Score	Lansky Play-Performance Scale Definitions (subjects ≤16)	Karnofsky Performance Scale Definitions (subjects > 16)
100	Fully active, normal	Normal; no complaints; no evidence of disease
90	Minor restrictions in physically strenuous activity	Able to carry on normal activity; minor signs or symptoms of disease
80	Active, but tires more quickly	Normal activity with effort; some signs or symptoms of disease
70	Both greater restriction of, and less time spent in, active play	Care of self; unable to carry on normal activity or to do active work
60	Up and around, but minimal active play; keeps busy with quieter activities	Requires occasional assistance but is able to care for most of his needs
50	Gets dressed but lies around much of the day, no active play; able to participate in all quiet play and activities	Requires considerable assistance and frequent medical care
40	Mostly in bed; participates in quiet play activities	Disabled; requires special care and assistance
30	In bed; needs assistance even for quiet play	Severely disabled; hospitalization is indicated although death not imminent
20	Often sleeping; play entirely limited to very passive activities	Hospitalization necessary, very sick active supportive treatment necessary
10	No play; does not get out of bed	Moribund; fatal processes progressing rapidly
0	Unresponsive	Dead

12.5 Emetogenicity of Commonly Used Chemotherapeutic Agents

MINIMAL RISK (<10% frequency)	LOW RISK (10-<30% frequency)	MODERATE RISK (30-90% frequency)	HIGH RISK* (>90% frequency)
Alemtuzumab	Amifostine ≤ 300 mg/m^2	Aldesleukin > 12 to 15 million units/ m^2	**Single agent antineoplastic therapy**
Alpha interferon	Amsacrine	Amifostine >300 mg/m^2	Altretamine
Aspagarinase (IM or IV)	Bexarotene	Arsenic trioxide	Carboplatin
Bevacizumab	Busulfan (oral)	Azacitidine	Carmustine >250 mg/m^2
Bleomycin	Capecitabine	Bendamustine	Cisplatin
Bortezomib	Cytarabine ≤ 200 mg	Busulfan	Cyclophosphamide ≥1 g/m^2
Cetuximab	Docetaxel	Carmustine ≤ 250 mg/m^2	Cytarabine 3 g/m^2/dose
Chlorambucil (oral)	Doxorubicin (liposomal)	Clofarabine	Dacarbazine
Cladribine (2-chlorodeoxyadenosine)	Etoposide	Cyclophosphamide <1 g/m^2	Dactinomycin
Dasatinib	Fludarabine (oral)	Cyclophosphamide (oral)	Mechlorethamine
Decitabine	5-Fluorouracil	Cytarabine > 200 mg to <3 g/m^2	Methotrexate ≥12 g/m^2
Denileukin diftitox	Gemcitabine	Daunorubicin	Procarbazine (oral)
Dexrazoxane	Ixabepilone	Doxorubicin	Streptozocin
Erlotinib	Methotrexate >50 mg/m^2 to <250 mg/m^2	Epirubicin	Thiotepa ≥ 300 mg/ m^2
Fludarabine	Mitomycin	Etoposide (oral)	**Multiple agent antineoplastic therapy**
Gefitinib	Mitoxantrone	Idarubicin	Cyclophosphamide + anthracycline
Gemtuzumab ozogamicin	Nilotinib	Ifosfamide	Cyclophosphamide + doxorubicin
Hydroxyurea (oral)	Paclitaxel	Imatinib (oral)	Cyclophosphamide + epirubicin
Lapatinib	Paclitaxel-albumin	Intrathecal therapy (methotrexate, hydrocortisone & cytarabine)	Cyclophosphamide + etoposide
Lenalidomide	Pemetrexed	Irinotecan	Cytarabine 150-200 mg/ m^2 + daunorubicin
Melphalan (oral low-dose)	Teniposide	Lomustine	Cytarabine 300 mg/ m^2 + etoposide
Mercaptopurine (oral)	Thiotepa < 300 mg/ m^2	Melphalan > 50 mg/ m^2	Cytarabine 300 mg/ m^2 + teniposide
Methotrexate ≤ 50 mg/ m^2	Topotecan	Methotrexate ≥ 250 mg/m^2 to <12 g/m^2	Doxorubicin + ifosfamide
Nelarabine	Vorinostat	Oxaliplatin >75 mg/m^2	Doxorubicin + methotrexate 5 g/ m^2
Panitumumab		Temozolomide (oral)	Etoposide + ifosfamide
Pentostatin		Vinorelbine (oral)	
Rituximab			
Sorafenib			
Sunitinib			
Temsirolimus			
Thalidomide			
Thioguanine (oral)			
Trastuzumab			
Valrubicin			
Vinblastine			
Vincristine			
Vindesine	* Except for combinations of agents listed below, emetogenicity is classified based on the most highly emetogenic agent.		
Vinorelbine			

Note: All agents given intravenously (IV) unless stated otherwise.
Adapted from Dupuis, L et al Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients. Pediatric Oncology Group of Ontario;Toronto. 2012.

12.6 Approximate Blood Volumes Drawn by Trial Visit and by Sample Types

	Cycle 1			Cycle 2
Trial Visit:	**Screening Visit 1**	**Randomization Visit 2**	**Follow-Up/Disc. Visit 4**	**Treatment**
Blood Parameter	*Approximate Blood Volume (mL)*			
Hematology	~0.5		~ 0.5	
Chemistry	~0.6		~0.6	
Ionized Calcium (at selected sites)	(~0.6)	(~0.6)		
PK for aprepitant				~2.0 (~0.5 at 4 time points)
Expected Total (mL)	~1.1 (~1.7)	(~0.6)	~1.1	~2.0

12.7 Abbreviations and Definitions

Abbreviation	Definition
Acute Phase	0 to 24 hours following initiation of emetogenic chemotherapy
5-HT$_3$	5-hydroxytryptamine 3
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC$_{0-\infty}$	Area under the concentration-time curve from time 0 to infinity
CINV	Chemotherapy-induced nausea and vomiting
C_{max}	Maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
Complete Response	No vomiting, no retching, and no use of rescue medication
CRF	Case report form
CSR	Clinical study report
CYP	Cytochrome P450
Delayed Phase	>24 to 120 hours following initiation of chemotherapy infusion
DNA	Deoxyribonucleic acid
Dry Heaves	When the subject tries to vomit and nothing comes up (as defined in the Patient Diary); Used synonymously with retching
ECG	Electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic case report form
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
GCP	Good clinical practice
HEC	Highly emetogenic chemotherapy
IB	Investigator's brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
MASCC	Multinational Association of Supportive Care in Cancer
MEC	Moderately emetogenic chemotherapy
Nausea	feeling the need to vomit

Abbreviation	Definition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK_1	Neurokinin-1
No Rescue Medication	Subject did not use medication to relieve symptoms of nausea or vomiting
No Vomiting	No vomiting and no retching/dry heaves (regardless of use of rescue medication)
Overall Phase	0 to 120 hours following initiation of emetogenic chemotherapy
PD	Pharmacodynamic(s)
PGt	Pharmacogenetic
PK	Pharmacokinetic(s)
PONV	Post-operative nausea and vomiting
PP	Per protocol
Prophylactic Medication	Medication to prevent symptoms of anticipated nausea and vomiting
QT	QT interval (interval between the Q and T waves in an electrocardiogram)
Rescue Medication	Medication to relieve symptoms of established nausea or vomiting
Retching	When subject tries to vomit and nothing comes up; Used synonymously with dry heaves
RNA	Ribonucleic acid
SAP	Statistical analysis plan
SAE	Serious Adverse Event
SOC	System organ class
T_{zero}	Start date and time of chemotherapy infusion
ULN	Upper limit of normal
Vomiting	When the contents of the stomach come up and out through the mouth (as defined in the Patient Diary)

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	