Official Protocol Title:	A Phase 4, Open-label, Single Arm Study to Evaluate the Safety and Tolerability of a Three-day Fosaprepitant Regimen Administered for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Participants Receiving Emetogenic Chemothera
NCT number:	NCT04054193
Document Date:	17-NOV-2020

Title Page

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Protocol Title: A Phase 4, Open-label, Single Arm Study to Evaluate the Safety and Tolerability of a Three-day Fosaprepitant Regimen Administered for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Participants Receiving Emetogenic Chemotherapy

Protocol Number: 045-00

Compound Number: MK-0517

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

EudraCT	2018-004844-43

Approval Date: 11 April 2019

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 4, Open-label, Single Arm Study to Evaluate the Safety and Tolerability of a Three-day Fosaprepitant Regimen Administered for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Participants Receiving Emetogenic Chemotherapy

Short Title: Three-day Fosaprepitant Regimen CINV Safety Study in Pediatric Participants

Hypotheses, Objectives, and Endpoints:

No formal hypothesis testing will be conducted in this study.

In male and female participants aged 6 months to 17 years of age (inclusive) receiving emetogenic chemotherapy:

Primary Objectives	Primary Endpoints
- Objective: To evaluate the safety and tolerability of the 3-day fosaprepitant regimen.	- Adverse events (AEs) - Discontinuation of study intervention due to AEs

Overall Design:

Study Phase	Phase 4
Primary Purpose	Prevention
Indication	Prevention of nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic chemotherapy in pediatric participants.
Population	Pediatric participants receiving emetogenic chemotherapy for a documented malignancy.
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded Open-label

Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 19 months from the time the first participant signs the informed consent/assent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 100 participants will be allocated and evaluated for safety.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin	Treatment Period	Use
Fosaprepitant Regimen	Fosaprepitant dimeglumine	Participants 12 to 17 years of age: Day 1: 115 mg Days 2 and 3: 80 mg Participants 6 months to <12 years of age: Day 1: 3.0 mg/kg Days 2 and 3: 2.0 mg/kg	Once daily for 3 days	IV Infusion	Days 1 to 3	Investigational Product
	5-HT_3 antagonist	Per product label or standard of care.	Per product label or standard of care.	Investigator discretion	Required on Day 1. Use after Day 1 is at the discretion of the investigator.	Background Treatment
	Dexamethasone (optional)[a]	Per product label or standard of care.	Per product label or standard of care.	Investigator discretion, provided dose reduction achievable.	Use is at the discretion of the investigator.	Background Treatment

5-HT_3=5-hydroxytryptamine 3; admin=administration; IV=intravenous.
[a] When administered concomitantly with fosaprepitant, the dose of dexamethasone should be reduced to 50% of the usual prescribed dose. This 50% dose reduction applies to dexamethasone used prophylactically and as rescue medication. Dexamethasone dose reduction is required on each day of fosaprepitant administration and for 24 hours following the last dose of fosaprepitant (ie, dose reduction required Days 1 to 4).

Total Number	1
Duration of Participation	Each participant will participate in Cycle 1 for approximately 45 days from the time the Informed Consent Form (ICF) is signed through the final contact. After a screening period of up to 28 days, each participant will be receiving assigned intervention for 3 days. After the end of treatment each participant will be followed for 14 days. **Note:** Participants may have the option to participate in up to 2 additional open-label cycles. Each optional cycle will be approximately 17 days.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
There are no governance committees in this study.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 12.

1.2 Schema

The study design is depicted in Figure 1.

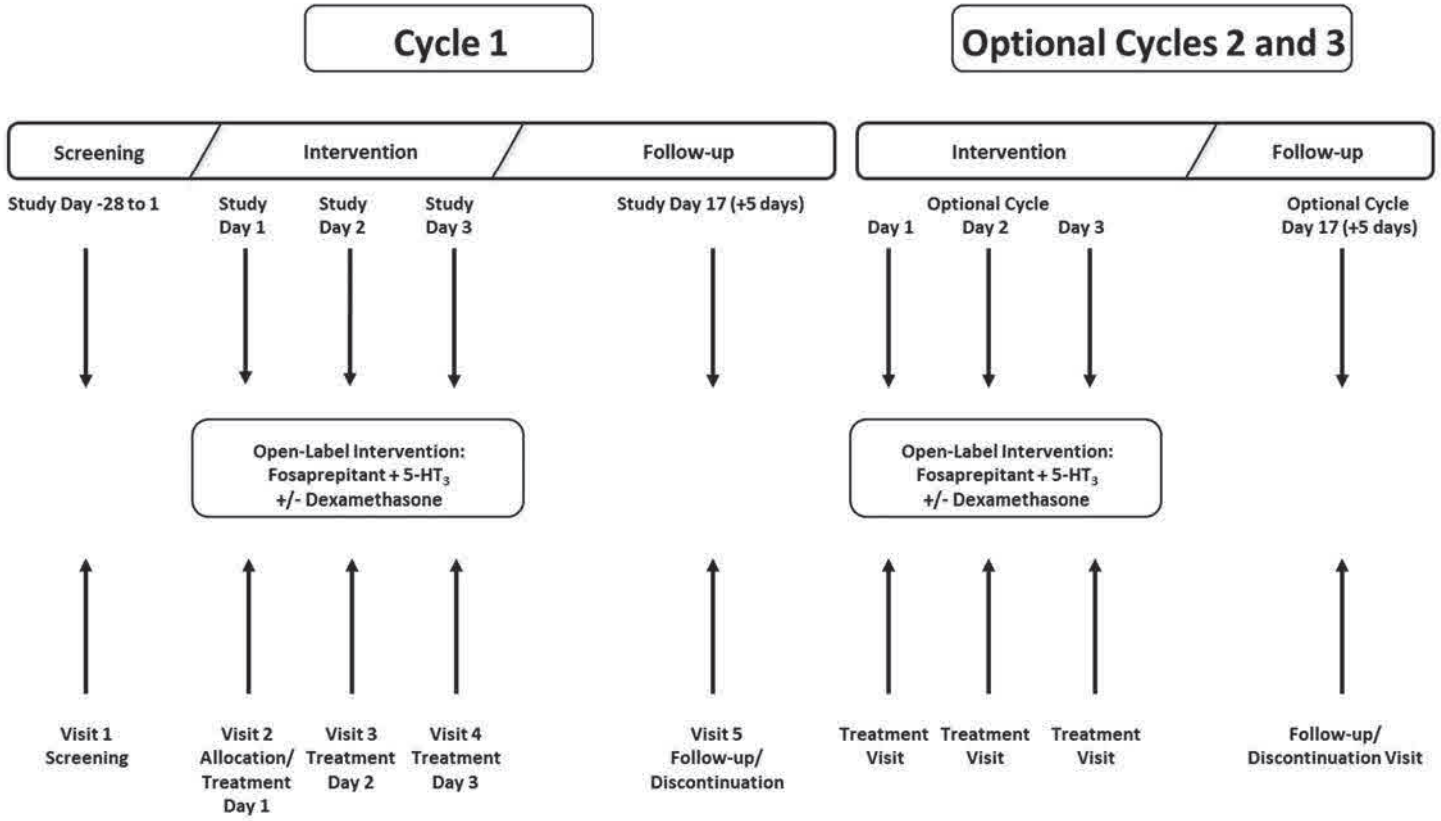

Figure 1 Study Design

1.3 Schedule of Activities (SoA)

Cycle 1 **Refer to Section 8 for details and timing of study assessments and procedures.**						
Study Period	Screening	Intervention			Follow-up	Notes
Visit Number/Title	1 Screening	2 Study Allocation/ Treatment Day 1	3 Treatment Day 2	4 Treatment Day 3	5 Follow-up/ Discontinuation	
Study Day (Visit Window)	-28 to 1	1	2	3	17 (+5 days)	
Administrative and General Procedures						
Informed Consent and Assent (if applicable)	X					
Inclusion/Exclusion Criteria	X	X				
Participant Identification Card	X (dispense)				X (collect)	Collect if participant discontinues during Cycle 1 or is not participating in optional cycle(s).
Medical History	X	X				Prior to study allocation.
Prior Medication Review	X	X				
Concomitant Medication Review		X	X	X	X	
Assignment of Screening and Study Allocation Numbers	X	X				
Register Study Visit and/or Dispense Study Intervention via IRT	X	X			X	Register discontinuation visit if participant discontinues during Cycle 1 or is not participating in optional cycle(s).
Laboratory and/or ECG Safety Test Review	X	X			X	Screening laboratory and ECG results must be reviewed prior to study allocation.
Fosaprepitant Administration		X	X	X		
5-HT_3 Antagonist Administration		X	X	X		Use on Day 1 is required. Use after Day 1 is at the discretion of the investigator.
Optional Dexamethasone Administration		X	X	X		Use is at the discretion of the investigator. See Section 6.2.1.3.

Cycle 1 **Refer to Section 8 for details and timing of study assessments and procedures.**						
Study Period	Screening	Intervention			Follow-up	Notes
Visit Number/Title	1 Screening	2 Study Allocation/ Treatment Day 1	3 Treatment Day 2	4 Treatment Day 3	5 Follow-up/ Discontinuation	
Study Day (Visit Window)	-28 to 1	1	2	3	17 (+5 days)	
Chemotherapy Infusion		X	X	X		Use on Day 1 is required. Use after Day 1 is at the discretion of the investigator.
Safety Assessments						
Full Physical Examination	X					
Directed Physical Examination					X	
Height		X				Prior to study intervention administration.
Weight	X	X				
Vital Signs (HR, BP, RR, Axillary/Oral/Rectal/Temporal /Tympanic Temp)	X	X	X	X	X	
Vital Signs (HR and BP)		X	X	X		Measure ~15 minutes after completion of fosaprepitant infusion and prior to chemotherapy initiation.
12-lead ECG	X				X	Screening ECG must be completed within the 7 days prior to study intervention administration on Day 1. See Section 8.3.6.
Lansky or Karnofsky Performance Status Evaluation	X					
Laboratory Safety Evaluations (Hematology, Chemistry)	X				X	Screening laboratory safety evaluations must be completed within the 7 days prior to study intervention administration on Day 1. See Section 8.3.8.1.
Urine Pregnancy Test (WOCBP only)	X					Complete within 7 days prior to study intervention administration on Day 1. See Section 8.3.8.2.

Cycle 1 **Refer to Section 8 for details and timing of study assessments and procedures.**						
Study Period	Screening	Intervention			Follow-up	Notes
Visit Number/Title	1 Screening	2 Study Allocation/ Treatment Day 1	3 Treatment Day 2	4 Treatment Day 3	5 Follow-up/ Discontinuation	
Study Day (Visit Window)	-28 to 1	1	2	3	17 (+5 days)	
Adverse Event Monitoring	X----------X					In Cycle 1, record all AEs, SAE(s), and other reportable safety events.

5-HT_3=5-hydroxytryptamine 3; AE=adverse event; BP=blood pressure; ECG=electrocardiogram; ECI=event of clinical interest; HR=heart rate; IRT=Interactive Response Technology; NSAE=nonserious adverse event; RR=respiratory rate; SAE=serious adverse event; temp=temperature; WOCBP=women of childbearing potential.

Cycles 2 and 3 **Refer to Section 8 for details and timing of study assessments and procedures.**					
Study Period	Intervention			Follow-up	Notes
Visit Title	Treatment Day 1	Treatment Day 2	Treatment Day 3	Follow-up/ Discontinuation	
Study Day (Visit Window)	1	2	3	17 (+5 days)	
Administrative and General Procedures					
Informed Consent and Assent (if applicable)	X				Prior to start of Cycle 2 only.
Inclusion/Exclusion Criteria	X				Prior to study intervention administration.
Participant Identification Card				X (collect)	
Concomitant Medication Review	X			X	
Register Study Visit and/or Dispense Study Intervention via IRT	X			X	Register discontinuation visit when participant discontinues from the study.
Fosaprepitant Administration	X	X	X		
5-HT_3 Antagonist Administration	X	X	X		Use on Day 1 is required. Use after Day 1 is at the discretion of the investigator.
Optional Dexamethasone Administration	X	X	X		Use is at the discretion of the investigator. See Section 6.2.1.3.
Chemotherapy Infusion	X	X	X		Use on Day 1 is required. Use after Day 1 is at the discretion of the investigator.
Safety Assessments					
Directed Physical Examination	X			X	Prior to study intervention administration.
Weight	X				
Vital Signs (HR, BP, RR, Axillary/Oral /Rectal/Temporal/Tympanic Temp)	X	X	X	X	
Vital Signs (HR and BP)	X	X	X		Measure ~15 minutes after completion of fosaprepitant infusion and prior to chemotherapy initiation.
Urine Pregnancy Test (WOCBP only)	X				Complete within 7 days prior to study intervention administration on Day 1 of Cycles 2 and 3. See Section 8.3.8.2.
Adverse Event Monitoring	X----------X				In Cycles 2 and 3, record all SAE(s), drug-related AE(s), AE(s) leading to discontinuation from study intervention, and other reportable safety events.

5-HT_3=5-hydroxytryptamine 3; AE=adverse event; BP=blood pressure; ECI=event of clinical interest; HR=heart rate; IRT=Interactive Response Technology; NSAE=nonserious adverse event; RR=respiratory rate; SAE=serious adverse event; temp=temperature; WOCBP=women of childbearing potential.

2 INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) continues to be one of the most undesirable side effects in patients undergoing cancer treatment. In addition to lowering quality of life, CINV can potentially delay or reduce the dosage and number of planned chemotherapy regimens for subsequent cycles. CINV occurs more frequently in children receiving emetogenic chemotherapy than adults, with 70% to 95% of pediatric patients in one study reporting nausea and/or vomiting in the delayed phase [Vol, H., et al 2016] and 18% to 24% in the acute phase [Dupuis, L. L. and Nathan, P. C. 2003] [Foot, A. B. M. and Hayes, C. 1994].

The pathophysiology of CINV is similar in adults and children, resulting from activation of neurotransmitter receptors in the chemoreceptor trigger zone by certain chemotherapeutic agents [Aziz, F. 2012]. In adults and children, brain penetrant neurokinin-1 (NK_1)-receptor antagonists, such as aprepitant and fosaprepitant, have been shown to be clinically effective in preventing acute (0 to 24 hours following initiation of chemotherapy) and delayed (25 to 120 hours following initiation of chemotherapy) nausea and vomiting associated with emetogenic chemotherapy [Hesketh, P. J., et al 2003] [Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Ma GJ, et al. 2003] [Warr, D. G., et al 2005].

Oral EMEND™ (aprepitant, Merck) is a potent and selective NK_1 receptor antagonist that is highly effective in the prevention of nausea and vomiting due to highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) [Hesketh, P. J., et al 2003] [Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Ma GJ, et al. 2003] [Warr, D. G., et al 2005] [Rapoport, Bernardo, et al 2010]. Aprepitant is approved for the prevention of nausea and vomiting associated with initial and repeat courses of HEC and MEC in oncology patients 6 months and older. Because of its consistent demonstration of clinical benefit, aprepitant in combination with a 5-hydroxytryptamine 3 ($5\text{-}HT_3$) receptor antagonist and a corticosteroid is considered standard of care and recommended by the Multinational Association of Supportive Cancer Care (MASCC)/ European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) in adults and children for the prevention of CINV associated with HEC and MEC [Roila, F., et al 2016] [Dupuis, L. L., et al 2016] [National Comprehensive Cancer Network 2018] [Hesketh, P. J., et al 2017]. However, the inherent difficulty of administering oral medications to children is often compounded by additional factors in pediatric cancer patients, such as anticipatory CINV and chemotherapy-related odynophagia and mucositis. Thus, there was an ongoing need to evaluate intravenously (IV) administered antiemetic agents, such as fosaprepitant, that offer more convenient dosing and potentially improved adherence to recommended prophylaxis regimens.

Fosaprepitant dimeglumine (EMEND™ for injection), hereafter referred to as ‘fosaprepitant’, is a phosphoryl prodrug that is systemically converted to aprepitant within 30 minutes of intravenous administration. Therefore, efficacy following fosaprepitant administration can be expected to be derived from exposure to aprepitant. A 1-day regimen of 150-mg IV fosaprepitant in combination with other antiemetic agents, including a $5\text{-}HT_3$ receptor antagonist and a corticosteroid, has been approved worldwide for the prevention of HEC and MEC in adults.

The fosaprepitant pediatric development program consisted of one Phase 1 study (Protocol 134), one Phase 2b study (Protocol 029), and one Phase 3 study (Protocol 044) designed to demonstrate efficacy, safety, and tolerability of fosaprepitant for the prevention of nausea and vomiting as a 1-day IV fosaprepitant regimen in children receiving HEC or MEC. While the pediatric fosaprepitant program was ongoing, data from the 3-day oral aprepitant program demonstrated that NK_1 receptor blockade with aprepitant has similar antiemetic effects in children as in adults, confirming the ability to extrapolate the efficacy of a 1-day IV fosaprepitant regimen in pediatric patients from that demonstrated in adults. Modeling and simulation was used to derive a single dose regimen to match pharmacokinetic (PK) exposures associated with the adult 150-mg IV dose. Accordingly, Protocol 044 was discontinued.

Given that children are more likely to be treated with emetogenic chemotherapy over multiple consecutive days as compared to adults, a 3-day fosaprepitant regimen was also developed. The efficacy of the 3-day fosaprepitant regimen can be predicted from that demonstrated with the pediatric 3-day oral aprepitant regimen, given that the in vivo activity of fosaprepitant is attributable to aprepitant. Available aprepitant and fosaprepitant PK data were used to derive a 3-day fosaprepitant regimen able to achieve similar exposures as the approved pediatric 3-day oral aprepitant regimen. Modeling and simulation also demonstrated that oral aprepitant or IV fosaprepitant could be used interchangeably on Days 2 and 3, to provide dosing flexibility.

The safety data collected across the pediatric fosaprepitant and aprepitant programs demonstrate that fosaprepitant is generally well tolerated with an adverse event (AE) profile typical of a population of pediatric patients with cancer receiving emetogenic chemotherapy. Pooled safety data from pediatric patients receiving a single dose of fosaprepitant at or above the highest proposed daily doses in the 3-day regimen support the safety of the 3-day IV regimen. Furthermore, as fosaprepitant is rapidly and completely converted to aprepitant, the safety and tolerability of the currently approved pediatric 3-day oral aprepitant regimen supports that fosaprepitant can be safely administered for 3 consecutive days without accumulation that would increase daily aprepitant maximum observed plasma concentration (C_{max}) beyond that associated with the safety and tolerability established across the pediatric clinical program.

Based on these data, fosaprepitant has been approved for use in the European Union (EU) as a single-day (1-day) or 3-day IV/IV/IV regimen (consecutive daily IV administration on Days 1 to 3; hereafter referred to as the '3-day IV fosaprepitant regimen') for children 6 months to 17 years of age, with flexibility to use oral aprepitant or IV fosaprepitant on Days 2 and 3. In the United States (US), fosaprepitant has been approved for children 6 months to 17 years of age as a 1-day fosaprepitant regimen, or a combined IV/oral 3-day regimen, with fosaprepitant injection on Day 1 followed by oral aprepitant on Days 2 and 3.

2.1 Study Rationale

Although the 3-day IV fosaprepitant regimen was not directly evaluated in the clinical development program, safety data across the fosaprepitant and aprepitant studies support its safety and tolerability. This study is being conducted to collect additional data to describe the

safety and tolerability of multiple cycles of IV administration of fosaprepitant daily for 3 consecutive days, concomitantly with a 5-HT_3 antagonist, with or without dexamethasone, to provide direct evidence to further support the safety of the 3-day IV/IV/IV regimen.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

The aprepitant and fosaprepitant IBs contain information about the physical, chemical, pharmaceutical, and formulation properties; preclinical and first in human studies; as well as clinical studies conducted with these compounds.

2.2.2 Information on Other Study-related Therapy

Current antiemetic guidelines recommend the use of a NK_1 receptor antagonist (such as aprepitant), plus a 5-HT_3 antagonist, plus dexamethasone for the prevention of nausea and vomiting associated with emetogenic chemotherapy in pediatric patients [Patel, P., et al 2017] [Dupuis, L. L., et al 2016] [Roila, F., et al 2016] [Hesketh, P. J., et al 2017]. Fosaprepitant is approved for use in pediatric patients as part of an antiemetic regimen that includes a 5-HT_3 antagonist and a corticosteroid for the prevention of CINV. Consistent with current guidelines and the fosaprepitant product label, this study will evaluate fosaprepitant in combination with a 5-HT_3 antagonist, with or without dexamethasone.

The 5-HT_3 antagonist to be used in this study will be determined by the investigator. Use is required on Day 1. The dose and timing of administration will be determined by the investigator based on the product label or local standard of care. Use of a 5-HT_3 antagonist after Day 1 will be at the discretion of the investigator.

The use of dexamethasone as part of the antiemetic regimen in this study is at the discretion of the investigator. As both aprepitant and dexamethasone are substrates of cytochrome P450 3A4 (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 (area under the curve) and C_{max}. A study evaluating the effects of aprepitant on the PK of IV dexamethasone has, likewise, demonstrated comparable results [Nakade, S., et al 2008]. Thus, based upon available data, if dexamethasone is administered as part of the standard antiemetic regimen for participants receiving fosaprepitant, the dose of dexamethasone should be reduced to 50% of the usual prescribed dose when administered within 24 hours following administration of fosaprepitant. This dose reduction applies to dexamethasone used as part of the antiemetic regimen and as rescue medication. Any formulation of dexamethasone is permitted, if a proper dose reduction (50%) is achievable. The dose and timing of administration will be determined by the investigator based on the product label or local standard of care.

2.3 Benefit/Risk Assessment

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 and children, the benefit-to-risk assessment for conducting this study is favorable.

Aprepitant/fosaprepitant was generally safe and well tolerated in the pediatric development program (Protocols 097, 134, 208, 029, and 044). The overall AE profile in pediatric participants, including those receiving single doses of fosaprepitant equal to or higher than those to be evaluated as part of the 3-day IV regimen, was similar to that reported in adults and typical of a population receiving emetogenic chemotherapy. Available aprepitant and fosaprepitant PK data were used to derive the 3-day IV fosaprepitant regimen to achieve similar exposures as the approved pediatric 3-day oral aprepitant regimen. Thus, there is no expectation of increased safety risk for participants enrolled in this study.

Because fosaprepitant is rapidly and completely converted to aprepitant and the in vivo activity of fosaprepitant is attributable to aprepitant exposures, the efficacy of the 3-day IV fosaprepitant regimen in pediatric participants was established by bridging to that demonstrated in pediatric participants receiving the approved 3-day oral aprepitant regimen, given comparable exposures. Thus, the 3-day IV fosaprepitant regimen is expected to provide clinical benefit to study participants.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

No hypothesis testing will be conducted in this safety study.

In male and female participants aged 6 months to 17 years of age (inclusive) receiving emetogenic chemotherapy:

Objectives	Endpoints
Primary	
• Objective: To evaluate the safety and tolerability of the 3-day fosaprepitant regimen.	• Adverse events (AEs) • Discontinuation of study intervention due to AEs

4 STUDY DESIGN

4.1 Overall Design

This is a nonrandomized, single-group, multi-site, open-label study to evaluate the safety and tolerability of consecutive 3-day IV fosaprepitant (also known as MK-0517) for the prevention of CINV in pediatric participants scheduled to receive a moderately or highly emetogenic chemotherapy agent/regimen, or a chemotherapy agent/regimen not previously tolerated due to vomiting.

Approximately 100 participants will be enrolled across 4 age cohorts; 6 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to 17 years of age (inclusive). Efforts will be made to enroll approximately even numbers in each cohort, though the final enrollment in each age cohort may differ.

This study will evaluate single-daily doses of fosaprepitant administered over 3 consecutive days in combination with a 5-HT_3 antagonist. Participants will receive a single-dose of IV fosaprepitant, plus a 5-HT_3 antagonist on Day 1 of emetogenic chemotherapy. Following Day 1, participants will receive single-daily doses of IV fosaprepitant on Days 2 and 3, with or without a 5-HT_3 antagonist. Dexamethasone is permitted as part of the antiemetic regimen at the discretion of the investigator. Participants are required to be fosaprepitant naïve, permitted to be chemotherapy naïve or non-naïve, and are permitted to receive single-day or multiple-day chemotherapy. Study Cycle 1 does not need to coincide with the participant's first chemotherapy cycle for treatment of disease. Study Cycle 1 may occur at any point during the participant's treatment, provided all inclusion and exclusion criteria are satisfied.

The primary objective of this study will be assessed during a single chemotherapy cycle (Cycle 1). Upon completion of Cycle 1, eligible participants will be invited to participate in up to 2 additional cycles of chemotherapy where fosaprepitant will be administered and additional safety data will be collected. Participation in Cycles 2 and 3 is optional. Participants choosing to continue in Cycles 2 and 3 will be allowed a maximum of 3 months from the end of Cycle 1 to complete the additional cycles.

In Cycle 1, participants may be screened up to 28 days prior to allocation. Eligible participants will be allocated to study intervention and enter the intervention period. Day 1 of treatment will coincide with Day 1 of chemotherapy. Participants will receive open-label fosaprepitant on Days 1, 2, and 3 and will be followed for 14 days after the last treatment with fosaprepitant for assessment of safety. Participants will have up to 5 clinic visits.

Participants will be re-evaluated before entering optional Cycles 2 and 3 to determine if entry criteria have been met. If entry criteria are met, participants will enter the intervention period of the optional cycle and receive fosaprepitant in the same manner as Cycle 1 (fosaprepitant on Days 1, 2, and 3). Participants will be followed for 14 days after his/her last treatment with fosaprepitant in each study cycle. There are 4 clinic visits during each optional cycle.

The safety and tolerability of fosaprepitant will primarily be monitored by clinical assessment of AEs, discontinuation of study intervention due to AEs, and standard laboratory

tests. Additional study parameters, including vital signs, physical examination, electrocardiogram (ECG), and laboratory safety tests, will be inspected at time points specified in the Schedule of Activities (SoA).

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This is a post-approval study designed to provide direct clinical study experience with repeated daily administration of IV fosaprepitant as part of a 3-day IV/IV/IV regimen. Given the extent of data already collected across the aprepitant and fosaprepitant programs, and the specific objective to describe the AEs associated with the 3-day IV regimen, a comparator group is not planned.

The efficacy of the 3-day IV fosaprepitant regimen has been established by bridging from the pediatric 3-day oral aprepitant regimen, given that the in vivo activity of fosaprepitant is attributable to aprepitant. Hence, efficacy will not be assessed in this study.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Efficacy is not being evaluated in this study.

4.2.1.2 Safety Endpoints

The primary objective of this study is to evaluate the safety and tolerability of the 3-day IV regimen of fosaprepitant when administered concomitantly with a 5-HT_3 antagonist, with or without dexamethasone, in participants aged 6 months to 17 years receiving emetogenic chemotherapy for a documented malignancy.

Safety and tolerability endpoints in Cycle 1 will be assessed by evaluation of all clinical and laboratory AEs, including those that are considered drug-related, serious, serious drug-related, lead to discontinuation from study intervention, or other reportable safety events. In Cycles 2 and 3, all serious adverse events (SAEs), drug-related nonserious adverse events (NSAEs), AEs that lead to discontinuation from study intervention, and other reportable safety events will be recorded.

Safety and tolerability will also include assessment of additional study parameters including vital signs, physical examination, ECGs, and laboratory safety tests at time points specified in the SoA.

4.2.1.3 Pharmacokinetic Endpoints

PK parameters are not being evaluated in this study.

4.2.1.4 Pharmacodynamic Endpoints

Pharmacodynamic parameters are not being evaluated in this study.

4.2.2 Rationale for the Use of Comparator/Placebo

This is an open-label study, without a comparator or placebo. All participants will receive fosaprepitant plus a 5-HT_3 antagonist. Dexamethasone may be administered to all participants as part of the antiemetic regimen based on local standard of care or investigator discretion.

4.3 Justification for Dose

4.3.1 Rationale for Dose and Study Design

A pooled population PK analysis was conducted using fosaprepitant and aprepitant pediatric PK data (Protocols 097, 148, 134, 029), permitting an extensive characterization of aprepitant PK across the pediatric population in the setting of single- and 3-day IV fosaprepitant dosing regimens, as well as combination IV fosaprepitant and oral aprepitant regimens.

Simulations based on the population PK model were conducted to derive a pediatric single-day IV fosaprepitant regimen to match the adult PK exposures associated with safety and efficacy at the 150-mg IV dose. Similarly, modeling and simulation of PK data was applied to identify a 3-day fosaprepitant regimen, administered as IV or combination IV/oral formulations, for use in pediatric patients aged 6 months to 17 years of age to match exposures of the 3-day oral aprepitant regimen that demonstrated meaningful efficacy in children receiving emetogenic chemotherapy. In addition, the simulated PK parameters for the 3-day IV regimen are within the range associated with safety and tolerability in pediatric participants from all age cohorts. Similar to the 3-day oral aprepitant regimen, the 3-day IV fosaprepitant regimen to be evaluated in this study consists of a higher dose on Day 1 to maximize central nervous system NK_1 receptor occupancy, followed by reduced doses on Days 2 and 3 to maintain relatively consistent daily plasma trough concentrations over 3 days of dosing:

- Participants 6 months to <12 years of age: 3.0 mg/kg IV on Day 1, followed by 2.0 mg/kg IV on Days 2 and 3
- Participants 12 to 17 years of age: 115 mg IV on Day 1, followed by 80 mg IV on Days 2 and 3

This regimen is consistent with the approved pediatric dosing regimen in the EU for the prevention of CINV.

4.3.2 Rationale for Emetogenic Classification

The Pediatric Oncology Group of Ontario (POGO) developed the Emetogenicity Classification Framework Clinical Pediatric Guideline aimed at providing evidence-based recommendations on the emetogenic potential of chemotherapy agents and regimens specific for pediatric oncology patients [Paw Cho Sing, E., et al 2019]. This framework classifies single- and multiple-agent chemotherapy regimens as highly emetogenic (>90%), moderately emetogenic (30% to <90%), of low emetogenicity (10% to <30%), or minimally emetogenic (<10%) based on the frequency of emesis in the absence of prophylaxis.

For this study, the classification criteria developed by POGO will be used as a guide for participant enrollment. Participants who are administered a moderately or highly emetogenic chemotherapy agent/regimen based on the POGO criteria (see Appendix 8) or a chemotherapy agent/regimen not previously tolerated due to vomiting will be eligible to enroll in this study. If a planned chemotherapy agent/regimen is not listed in the Emetogenicity of Chemotherapeutic Agents and Regimens table (see Appendix 8), the investigator is encouraged to discuss the emetogenic stratification with the Sponsor Clinical Director.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent/assent form. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study 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 study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP), and/or other applicable regulatory requirements, procedure-related problems or an unacceptably high number of discontinuations or withdrawals due to administrative reasons.

5 STUDY POPULATION

Male and female participants who are scheduled to receive a moderately or highly emetogenic chemotherapy agent/regimen or a chemotherapy agent/regimen not previously tolerated due to vomiting for a documented malignancy between the ages of 6 months and 17 years (inclusive) will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

Type of Participant and Disease Characteristic

5.1.1 Inclusion Criteria for Cycle 1

1. Be receiving a moderately or highly emetogenic chemotherapy agent/regimen or a chemotherapy agent/regimen not previously tolerated due to vomiting. See Appendix 8 for guidance on the classification of the emetogenicity of chemotherapeutic agents and regimens.

2. Have a Lansky Play Performance score ≥60 (participants ≤16 years of age) or a Karnofsky score ≥60 (participants >16 years of age) as defined in Appendix 9.

3. Have a preexisting functional central venous catheter available for study intervention administration.

4. Be fosaprepitant naïve.

Demographics

5. Have a predicted life expectancy ≥3 months.

6. Be male or female.

   A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   - Is not a woman of childbearing potential (WOCBP)

     OR

   - Is a WOCBP and agrees to the following for at least 28 days prior to receiving study intervention, during the intervention period, and for at least 30 days (or local standard of care if longer) after the last dose of study intervention (including the optional cycles):

     - Not be sexually active which includes being abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) as described in Appendix 5.

       OR

- If sexually active, or if initiation of sexual activity occurs during the study, use a contraceptive method that is highly effective (with a failure rate of <1% per year) as described in Appendix 5. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) prior to the start of fosaprepitant administration in a given cycle. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are in Appendix 2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- A WOCBP must agree to add a barrier form of contraception (ie, male condom) to a hormonal contraception during the intervention period and for 30 days following the last dose of study intervention (or local standard of care if longer).

- The investigator is responsible for assuring that for a given participant, appropriate contraception requirements are followed if more stringent contraception is required for one of the non-study related medications that are being administered to treat the participant's cancer (ie, chemotherapeutic agents).

7. Be from 6 months to 17 years of age (inclusive) at the time of allocation.

8. Weigh at least 6 kg.

Informed Consent/Assent

9. Have parent/legal guardian (legally authorized representative) agreement to the participant's participation as indicated by parent/legal guardian signature on the ICF. Participants 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.

5.1.2 Inclusion Criteria for Optional Cycles 2 and 3

To be eligible for participation in an optional cycle, the participant must meet inclusion criteria 1, 3, and 6 above in addition to the 2 criteria below.

10. Have completed the preceding study cycle, have no unresolved drug-related AEs, and continued participation in an optional cycle poses no unwarranted risk to the participant as determined by the investigator.

11. Have parent/legal guardian (legally authorized representative) or participant (if participant is 18 years old) agreement to the participant's participation as indicated by parent/legal guardian or participant (if participant is 18 years old) signature on the ICF for the optional cycles. Participants 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.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

5.2.1 Exclusion Criteria for Cycle 1 Only

Medical Conditions

1. 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 × upper limit of normal (ULN) for age
    - alanine aminotransferase (ALT) >5.0 × ULN for age
    - bilirubin >1.5 × ULN for age
    - creatinine >1.5 × ULN for age

5.2.2 Exclusion Criteria for Cycle 1 and Optional Cycles 2 and 3

2. Will receive stem cell rescue therapy in conjunction with a study-related course of emetogenic chemotherapy or during the 14 days following administration of fosaprepitant.

3. Is currently a user of any recreational or illicit drugs or has current evidence of drug or alcohol abuse or dependence as determined by the investigator.

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

5. Is pregnant or breast feeding.

6. Is allergic to fosaprepitant, aprepitant, or prescribed 5-HT_3 antagonist.

7. Has an active infection (eg, pneumonia), congestive heart failure, bradyarrhythmia, any uncontrolled disease (eg, 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 intervention or concomitant therapy to the participant.

8. Is a WOCBP who has a positive urine pregnancy test at screening (Cycle 1) or on Day 1 of optional Cycles 2 or 3. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

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

   Exceptions:

   - Participant 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, participant is permitted to receive a single dose of corticosteroid within 3 days prior (but not on the days of study intervention administration) provided it is less than the equivalent of 20 mg of prednisone.

10. 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 the last dose of fosaprepitant in a given cycle.

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

Table 1 Excluded Medications

	Participant is **currently taking** or has taken within **30 days** of Treatment Day 1 in a given cycle **OR** is expected to receive within **120 hours** following the last dose of fosaprepitant in a given cycle.	Participant is **currently taking** or has taken within **7 days** of Treatment Day 1 in a given cycle **OR** is expected to receive within **120 hours** following the last dose of fosaprepitant in a given cycle.	Participant is **currently taking OR** is expected to receive within **2 weeks** following the last dose of fosaprepitant in a given cycle.
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.

Prior/Concurrent Clinical Study Experience

11. 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: Participants 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.

Diagnostic Assessments

12. Has a known history of QT prolongation or is taking any medication that is known to lead to QT prolongation.

5.3 Lifestyle Considerations

There are no lifestyle and/or dietary restrictions.

5.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies will be packaged to support enrollment . Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin istration	Treatment Period	Use	IMP/ NIMP	Sourcing
Fosaprepitant Regimen	Experi mental	Fosaprepitant dimeglumine	Drug	Vial	Day 1: 115 mg or age-specific dose adjustment Days 2 and 3: 80 mg or age-specific dose adjustment	Participants 12 to 17 years of age: Day 1: 115 mg Days 2 and 3: 80 mg Participants 6 months to <12 years of age: Day 1: 3.0 mg/kg Days 2 and 3: 2.0 mg/kg	IV Infusion	Days 1 to 3	Investigational Product	IMP	Centrally by Sponsor
Fosaprepitant Regimen	Other	5-HT_3 antagonist	Drug	Investigator discretion	Per product label or standard of care	Per product label or standard of care	Investigator discretion	Required on Day 1. Use after Day 1 is at the discretion of the investigator	Background Treatment	NIMP	Locally by the study site, subsidiary, or designee
Fosaprepitant Regimen	Other	Dexamethasone (optional)*	Drug	Investigator discretion, provided dose reduction achievable	Per product label or standard of care	Per product label or standard of care	Investigator discretion, provided dose reduction achievable	Use is at the discretion of the investigator	Background Treatment	NIMP	Locally by the study site, subsidiary, or designee

5-HT_3=5-hydroxytryptamine 3; IMP=Investigational Medicinal Product; IV=intravenous; NIMP=Non-Investigational Medicinal Product.
* When administered concomitantly with fosaprepitant, the dose of dexamethasone should be reduced to 50% of the usual prescribed dose. This 50% dose reduction applies to dexamethasone used prophylactically and as rescue medication. Dexamethasone dose reduction is required on each day of fosaprepitant administration and for 24 hours following the last dose of fosaprepitant (ie, dose reduction required Days 1 to 4).
Note: Definitions of IMP and NIMP are based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

6.2.1.1 Fosaprepitant

Open-label fosaprepitant will be supplied by the Sponsor as a single-dose 150-mg vial of lyophilized powder for reconstitution. The site will supply its own source of normal saline (0.9% sodium chloride) to be utilized in the preparation of fosaprepitant. Preparation instructions are located in a Pharmacy Manual.

Participants will receive 115 mg (or age-specific dose adjustment) of fosaprepitant on Day 1 and 80 mg (or age-specific dose adjustment) of fosaprepitant on Days 2 and 3. The fosaprepitant dose and age-specific dose adjustments for participants 12 to 17 years and 6 months to <12 years, respectively, are summarized in Table 3.

Table 3 Fosaprepitant Dose by Age

	Age-Specific Dose and Dose Adjustment	
	12 to 17 years	**6 months to <12 years**
Day 1	115 mg	3.0 mg/kg[a]
Days 2 and 3	80 mg	2.0 mg/kg[a]
[a] Not to exceed 115 mg on Day 1 and 80 mg on Days 2 and 3.		

Note: Fosaprepitant is incompatible with any solutions containing divalent cations (eg, Ca^{++}, Mg^{++}), including Lactated Ringer's Solution and Hartmann's Solution.

6.2.1.2 5-HT_3 Antagonist

A locally sourced 5-HT_3 antagonist is required on Day 1 as part of the preventative antiemetic regimen. The 5-HT_3 antagonist to be used is at the discretion of the investigator and should be administered according to the product label or local standard of care.

6.2.1.3 Dexamethasone (Optional)

Dexamethasone may be administered as part of an antiemetic regimen at the investigator's discretion, but it is not required. When administered concomitantly with fosaprepitant, whether receiving the full fosaprepitant dose or an age-based dose adjustment, the dose of

dexamethasone should be reduced to 50% of the usual prescribed dose. This 50% dose reduction applies to dexamethasone used prophylactically and as rescue medication. Dexamethasone dose reduction is required on each day of fosaprepitant administration and for 24 hours following the last dose of fosaprepitant (ie, dose reduction required Days 1 to 4). Any locally sourced formulation of dexamethasone is permitted, provided a dose reduction (50%) is achievable.

The rationale for selection of doses to be used in this study is provided in Section 4.3.1.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study 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.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

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 study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment using Interactive Response Technology (IRT).

6.3.2 Stratification

Study allocation will be stratified according to the following factors:

1. Age on Day 1 of Cycle 1 (6 months to <2 years; 2 to <6 years; 6 to <12 years; or 12 to 17 years).

2. Emetogenic potential of planned emetogenic chemotherapy agent/regimen in Cycle 1 (highly emetogenic, moderately emetogenic, or low/minimally emetogenic).

   Note: Emetogenic potential of the chemotherapy agent or regimen will be assigned by the investigator according to the POGO emetogenicity guidelines in Appendix 8.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention 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 participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Listed below are specific restrictions for concomitant therapy during the study:

1. Medications that are prohibited prior to and during the study are identified in Section 5.2 Exclusion Criteria.

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

6.5.1 Rescue Medications and Supportive Care

Participants may be provided with a prescription for rescue medication according to investigator preference. If dexamethasone is used as rescue medication, the usual prescribed

dose of dexamethasone must be reduced by 50% on each day of fosaprepitant administration and for 24 hours following the last dose of fosaprepitant (Days 1 to 4) administration.

6.6 Dose Modification

No dose modifications are permitted.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.10.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.10 and Section 8.3.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

- The participant has a confirmed positive serum pregnancy test. The pregnancy will be followed to resolution.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent, and assent if applicable, from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study.If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent/assent is in place.

8.1.1.1 General Informed Consent/Assent

Consent/assent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent/assent 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 participant before participation in the study.

The initial informed consent/assent form, any subsequent revised written informed consent/assent form, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. 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 participant's dated signature or by the participant's legally acceptable representative's dated signature.

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

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent/assent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 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 study allocation and will include:

- Date/type of cancer diagnosis

- History of QT prolongation
- Allergies to fosaprepitant, aprepitant, or prescribed 5-HT_3 antagonist
- All active conditions
- All inactive conditions diagnosed within the previous 5 years

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review and record prior medication taken by the participant within 30 days before starting the study. The doses will not be recorded. For participants hospitalized during this period, only the discharge medications will be recorded.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant starting on Day 1 of a study cycle through 14 days following the last dose of 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.

Medications that are prohibited prior to and during the study are identified in Section 5.2 Exclusion Criteria. If there is a clinical indication for any medications specified in Section 5.2 Exclusion Criteria, refer to Section 6.5 for further guidance.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to study allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.12.1.1.

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

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive an allocation number. The allocation number identifies the participant for all procedures occurring after study allocation. Once an allocation number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than one allocation number.

After all required screening procedures have been completed and a participant's eligibility has been confirmed, the study allocation visit will be registered in IRT.

The participant identification card will be updated with the allocation number.

8.1.8 Laboratory and Electrocardiogram Safety Test Review

Prior to study allocation, ECG and laboratory safety test results, including a urine pregnancy test (for WOCPB), will be reviewed to confirm that the results are clinically acceptable and the participant meets the study requirements. If the participant's ECG, and blood and urine laboratory tests were not done within the preceding 7 days to the Allocation 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 the prescribed 5-HT_3 antagonist, consistent with the 5-HT_3 antagonist 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 ECGs performed after study intervention administration, any clinically significant changes should be recorded as AEs.

8.1.9 Study Intervention Administration

Administration of study intervention will be witnessed by the investigator and/or study staff. The total volume of fosaprepitant infused will be compared to the total volume prepared for the participant based on study day, age, and weight (if applicable) to determine compliance with study intervention.

8.1.9.1 Timing of Dose Administration

8.1.9.1.1 Fosaprepitant

Day 1:

Age 6 months to <12 years: At approximately 90 minutes prior to initiation of the first emetogenic chemotherapy, participants will be administered fosaprepitant via a central venous catheter over a period of approximately 60 minutes. The infusion will be complete approximately 30 minutes prior to chemotherapy initiation.

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

Days 2 and 3:

Participants will be administered fosaprepitant, via a central venous catheter, on Days 2 and 3 over approximately 60 minutes (6 months to <12 years) or approximately 30 minutes (12 years to 17 years), completing the infusion approximately 30 minutes prior to chemotherapy initiation. If no chemotherapy is administered on Days 2 or 3, administer fosaprepitant approximately 24 hours after the previous dose of fosaprepitant.

8.1.9.1.2 5-HT_3 Antagonist

The locally sourced 5-HT_3 antagonist will be administered per product label or local standard of care with the first dose administered prior to initiation of the first emetogenic chemotherapy on Day 1. Additional doses of the 5-HT_3 antagonist on Day 1 will be administered according to local standard of care. For multiple-day chemotherapy regimens, the 5-HT_3 antagonist may be administered after Day 1 at the discretion of the investigator.

8.1.9.1.3 Dexamethasone (Optional)

The locally sourced dexamethasone may be administered as part of an antiemetic regimen and will be administered per product label or local standard of care with the first dose administered no later than 30 minutes prior to initiation of the first emetogenic chemotherapy on Day 1. Participants receiving multiple-day chemotherapy regimens are permitted to receive preventative antiemetic treatment with dexamethasone after Day 1, if clinically indicated and consistent with local standard of care. When administered concomitantly with fosaprepitant, whether receiving the full fosaprepitant dose or an age-specific dose adjustment, the dose of dexamethasone should be reduced to 50% of the usual prescribed dose. This 50% dose reduction applies to dexamethasone used prophylactically and as rescue medication. Dexamethasone dose reduction is required on each day of fosaprepitant administration and for 24 hours following the last dose of fosaprepitant (ie, dose reduction required Days 1 to 4). Any locally sourced formulation of dexamethasone is permitted, provided a dose reduction (50%) is achievable.

8.1.9.1.4 Chemotherapy Infusion

Participants will receive at least one moderately or highly emetogenic chemotherapy agent/regimen or a chemotherapy agent/regimen not previously tolerated due to vomiting.

The chemotherapy agent/regimen will be administered per the local standard of care. The dose, start and stop date/time for all chemotherapy agents will be recorded by the site staff.

Single-day and multiple-day regimens are permissible. All participants are required to receive chemotherapy on Day 1.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the study period should be encouraged to continue to be followed for all remaining study visits for the applicable cycle as outlined in the SoA (Section 1.3) and Section 8.12.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Follow-up/Discontinuation visit for the applicable cycle should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4. Participants 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 8.12.1.4 and Section 8.12.2.2.

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.12 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

There are no efficacy/immunogenicity assessments in this study.

8.3 Safety Assessments

Details regarding specific safety assessments to be performed in this study are provided below.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Full Physical Examination – Cycle 1 Only

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard during the screening period. 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 at the Screening Visit (before receiving study intervention) should be recorded as medical history.

8.3.2 Directed Physical Examination

Physical examinations after the Screening Visit will be directed exams. The investigator or medically qualified designee (consist with local requirements) as per institutional standard will perform a symptom-focused exam as clinically indicated. New clinically significant abnormal findings found after receiving study intervention on Day 1 will be reported as AEs. If an allocated participant is discontinued for any reason, every attempt should be made to perform a final directed physical examination if indicated.

8.3.3 Height – Cycle 1 Only

Height will be obtained with the participant's shoes off. This activity must be completed prior to study intervention administration.

8.3.4 Weight

Body weight will be obtained with the participant's shoes off and jacket/coat removed. This activity must be completed prior to study intervention administration.

8.3.5 Vital Signs

The investigator or qualified designee will assess vital signs at each visit for all cycles. Vital signs include blood pressure, heart rate, respiratory rate, and axillary/oral/rectal/temporal/tympanic temperature. Blood pressure and heart rate measurements will be assessed with the participant in a seated, semi-recumbent, prone, or supine position. An appropriately sized blood pressure cuff will be used. At each treatment visit in a cycle (Days 1 to 3), blood pressure and heart rate measurements will be taken prior to and approximately 15 minutes after fosaprepitant infusion, prior to chemotherapy initiation. Every effort should be made to collect these measurements using the same arm and body position.

8.3.6 Electrocardiograms – Cycle 1 Only

A screening 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements). If the participant's screening ECG was not done within the preceding 7 days to study intervention administration on Day 1, it will be repeated. Participants will receive a repeat ECG at the Follow-up/Discontinuation Visit in Cycle 1.

8.3.7 Lansky or Karnofsky Performance Status Evaluation – Cycle 1 Only

The Lansky and Karnofsky Performance Status Scales (Appendix 9) will be used to evaluate if the participant meets the study inclusion criterion. The Lansky Play-Performance Scale and Karnofsky Performance Scale will be used to evaluate participants ≤16 years of age and

>16 years of age, respectively. Participants must have a score ≥60 to participate in this study Refer to Section 5.1.

8.3.8 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with Section 1.3 (SoA).

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.8.1 Laboratory Safety Evaluations (Hematology and Chemistry) – Cycle 1 Only

Laboratory safety evaluations will be performed by the local laboratory according to local procedures and results will be documented on the participant's chart. Pre-dose testing that is conducted more than 7 days prior to study intervention administration will be repeated and reviewed prior to study intervention administration in Cycle 1.

The total amount of blood to be drawn/collected over the course of the study (from the Screening Visit to Follow-up/Discontinuation Visit), including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 10.

8.3.8.2 Pregnancy Test

All WOCBP considered for participation, must be tested for pregnancy within 7 days prior to the first dose of study intervention in Cycle 1 and within 7 days prior to Day 1 of Cycles 2 and 3. If a urine test is positive or not evaluable, a serum test will be required. A negative pregnancy test is required prior to the start of study intervention administration in a cycle. Urine pregnancy testing should be repeated at subsequent visits if the participant 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.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed, but before intervention allocation must be reported by the investigator if they cause the participant to be excluded from the study or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

In Cycle 1, from the time of study allocation through 14 days following cessation of study intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator. Such events will be recorded at each examination on the AE case report forms/worksheets.

In Cycles 2 and 3, all SAE(s), drug-related AE(s), AE(s) leading to discontinuation from study intervention, and other reportable safety events will be recorded. This includes the time period from the completion of Cycle 1 through 14 days following cessation of study intervention in the participant’s last optional cycle and at each examination.

From the time of study allocation through 30 days following cessation of study intervention (including the optional cycles), all pregnancies and exposure during breastfeeding must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraphs must be reported immediately to the Sponsor if the event is considered drug-related.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 4.

Table 4 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)[a]	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

[a] All NSAEs are collected in Cycle 1 from the time of study allocation through 14 days following cessation of study intervention. In the optional cycles (Cycle 2 and Cycle 3), only drug-related NSAEs and NSAEs that result in discontinuation of study intervention are collected.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply wth country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study is reportable to the Sponsor.

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.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are not applicable to this study.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

- 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 study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

- Hypersensitivity or anaphylactic reactions (including anaphylaxis and anaphylactic shock). Refer to Appendix 11 for guidance in reporting the ECIs of hypersensitivity and anaphylactic reactions.

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

8.5 Treatment of Overdose

In this study, an overdose is any single dose higher than the prescribed dose for each age range.

There is no specific information on the treatment of overdose with fosaprepitant. In the event of overdose, fosaprepitant should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of fosaprepitant, drug-induced emesis may not be effective in cases of fosaprepitant overdose.

Treatment of overdose of other study treatments should follow the prescribed information in the relevant package insert(s).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.9 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.10 Biomarkers

Biomarkers are not evaluated in this study.

8.11 Health Economics Medical Resource Utilization and Health Economics

Health Economics Medical Resource Utilization and Health Economics are not evaluated in this study.

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3 (SoA). Specific procedure-related details are provided in Section 8.

8.12.1 Cycle 1

8.12.1.1 Screening (Visit 1)

Up to 28 days prior to allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. The Screening Visit can occur the same day as the Allocation Visit (Day 1), as long as participant eligibility is confirmed and all required study procedures for both visits are completed/reviewed prior to study intervention administration.

Written consent and assent (if applicable) must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant/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 study intervention except for the following:

- Laboratory safety, urine pregnancy, and ECG testing must be completed within 7 days prior to initiation of study intervention.

Participants 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 participant/parent/legal guardian has signed an informed consent/assent, but the participant is not allocated into the study, the investigator will collect information at the Screening Visit, including: basic demographics, inclusion/exclusion criteria, participant disposition, laboratory data, and AE information, as applicable. Unless otherwise directed, no other data need to be collected for these participants.

8.12.1.2 Allocation/Treatment (Visit 2/Day 1)

The Allocation Visit (Visit 2/Day 1) should begin approximately 2.5 hours prior to initiation of emetogenic chemotherapy to allow adequate time to perform all study required procedures as detailed in the SoA (Section 1.3).

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

Preliminary screening laboratory test results will be reviewed. If the participant's screening laboratory tests and ECG were obtained within the preceding 7 days, they will only need to be repeated if the participant's clinical status has changed. If the screening laboratory tests and ECG were completed >7 days prior to Visit 2 (Day 1), then they will be repeated.

The participant's height, weight, and vital signs will be collected and recorded prior to the initiation of the first dose of study intervention. Blood pressure and heart rate will also be collected and recorded approximately 15 minutes after completion of fosaprepitant infusion, prior to the start of chemotherapy.

8.12.1.3 Treatment (Visits 3 and 4)

Participants will be required to return to the study site on study Days 2 and 3 for administration of study intervention as described in Section 8.1.9. The participant/parent/caregiver will be asked if the participant has had any changes in their health or taken any medications since the previous visit and the information will be recorded. The participant's vital signs will be collected and recorded prior to the initiation of study intervention each day. Blood pressure and heart rate will also be collected and recorded approximately 15 minutes after completion of fosaprepitant infusion, prior to the start of chemotherapy.

8.12.1.4 Follow-up/Discontinuation (Visit 5)

The participant will be required to return to the study site once between study Days 17 to 22 (or 14 to 19 days following the last dose of study intervention). For participants 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 the last dose of study intervention.

At the Follow-up/Discontinuation Visit, a directed physical examination and ECG will be performed, vital signs will be assessed, and laboratory safety evaluations will be collected. The participant/parent/guardian will be questioned about use of concomitant medications, including reason for its use for the 14-day period following the last dose of study intervention. If concomitant medications have been taken, the name of the medication and the date taken will be recorded. If there has been an interval hospitalization, only the discharge medications will be recorded.

If a participant does not elect to participate in optional Cycles 2 and 3, a discontinuation visit will be registered in IRT and reasonable effort should be made to collect the participant identification card.

8.12.2 Optional Cycles 2 and 3

A participant who completes Cycle 1 will be invited to participate in optional Cycles 2 and 3. A participant may participate in a total of 2 optional cycles. Each participant will be allowed a maximum of 3 months from the end of Cycle 1 to complete the optional cycles.

A minimum of 16 days is required between Day 1 in a cycle and Day 1 in a subsequent cycle.

8.12.2.1 Treatment Visits

Parent/legal guardian of participants <18 years old or participants 18 years of age participating in the optional cycles must provide documented consent prior to the start of Cycle 2. Written assent from participants 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 as outlined in the SoA (Section 1.3) and participant's eligibility has been confirmed, the treatment visit will be registered in IRT for study intervention component ID assignment.

8.12.2.2 Follow-Up/Discontinuation Visit

The participant will be required to return to the study site once during study Days 17 to 22 (14 to 19 days following the last dose of study intervention) of an optional cycle. For participants 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 following the last dose of study intervention of the current cycle.

At the Follow-up/Discontinuation Visit a directed physical examination will be performed and vital signs will be assessed. The participant/parent/guardian will be questioned about use of concomitant medications, including reason for its use for the 14-day period following the last dose of study intervention. If concomitant medications have been taken, the name of the

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

If a participant does not elect to participate in any additional optional cycles, a discontinuation visit will be registered in IRT. A participant who has completed the 2 optional cycles will have completed the study. Reasonable effort should be made to collect the participant identification card when a participant discontinues from or completes the study.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan (SAP) are summarized below. The comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A Phase 4, Open-label, Single Arm Study to Evaluate the Safety and Tolerability of a Three-day Fosaprepitant Regimen Administered for the Prevention of CINV in Pediatric Participants Receiving Emetogenic Chemotherapy
Treatment Assignment	Single Arm, Unblinded, Open-label
Analysis Populations	Efficacy: Not applicable for this safety study. Safety: All Participants as Treated (APaT).
Primary Endpoint(s)	• AEs • Discontinuation of study intervention due to AEs
Key Secondary Endpoints	There are no key secondary endpoints in this study.
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	Not applicable for this safety study.
Statistical Methods for Key Safety Analyses	This is a single treatment arm safety study. In Cycle 1, proportions will be displayed for AEs, SAE(s), drug-related AE(s), and AE(s) leading to discontinuation from study intervention which occur during the fosaprepitant treatment period plus 14 days post last dose of study intervention. For optional Cycles 2 and 3, proportions will be displayed for SAE(s), drug-related AE(s), and AE(s) leading to discontinuation from study intervention which occur during the fosaprepitant treatment period plus 14 days post last dose of study intervention.
Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	No multiplicity adjustment is planned for this study.
Sample Size and Power	The planned sample size is 100 participants.

9.2 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 and optional Cycles 2 and 3 of this study are being conducted as a non-randomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treated.

Results from all 3 cycles of chemotherapy will be presented in the CSR.

9.3 Hypotheses/Estimation

There will be no hypotheses/estimation for this safety study.

9.4 Analysis Endpoints

This is a safety study; therefore, efficacy data will not be collected. Safety data will be evaluated in all cycles.

9.4.1 Safety Endpoints

Safety endpoints in Cycle 1 will be assessed by evaluation of all clinical and laboratory AEs, including those that are considered drug-related, serious, serious drug-related, lead to discontinuation from study intervention, or other reportable safety events.

Safety endpoints in Cycles 2 and 3 will be assessed by evaluation of all SAEs, drug-related AEs, AEs that lead to discontinuation from study intervention, and other reportable safety events.

Safety and tolerability will also include assessment of additional study parameters including vital signs, physical examination, ECGs, and laboratory safety tests.

9.5 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all allocated participants who received at least one dose of study intervention.

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

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

There will be no efficacy analyses in this study.

9.6.2 Statistical Methods for Safety Analyses

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

The broad clinical and laboratory AE categories consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE which is both serious and drug-related, or who discontinued study intervention due to an AE will be summarized with descriptive statistics. AEs (specific as well as system organ class [SOC]) and continuing measures such as changes from baseline in laboratory tests (ALT, albumin, alkaline phosphatase [ALP], AST, bilirubin, creatinine, glucose, potassium, sodium, leukocytes, hemoglobin, neutrophils, and platelets), vital signs (heart rate, blood pressure [systolic and diastolic], and respiratory rate), and ECG (PR interval, QTc interval Bazett, and QTc interval Fridericia) parameters, will be provided in table format (Table 5).

Table 5 Analysis Strategy for Safety Parameters

Safety Endpoints	Descriptive Statistics
Any AE	X
Any Serious AE	X
Any Drug-Related AE	X
Any Serious and Drug-Related AE	X
Discontinuation of Study Intervention due to AE	X
Discontinuation of Study Intervention due to a Drug-Related AE	X
Specific AEs, SOCs	X
Change from Baseline Results (Labs, ECGs, Vital Signs)	X

AE=adverse event; ECGs=electrocardiograms; SOC=system organ class; X=results will be provided.

9.6.3 Demographic and Baseline Characteristics

For each relevant demographic and baseline characteristic, descriptive statistics will be assessed using tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, allocated, the primary reasons for screening failure, and primary reasons for discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical table.

9.7 Interim Analyses

No interim analyses are planned for this study.

9.8 Multiplicity

No multiplicity adjustment is planned for this study.

9.9 Sample Size and Power Calculations

The planned sample size is 100 participants. With a sample size of 100 participants, if the underlying incidence rate is 1% then the probability of observing ≥1 AE is 0.63; furthermore, if the underlying incidence rate is 5% then the probability of observing ≥1 AE is 0.99.

9.10 Subgroup Analyses

All results will be displayed by 4 age cohorts (6 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to 17 years).

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure (dose and duration) to fosaprepitant will be summarized by the number of participants exposed to fosaprepitant for defined periods of time.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants 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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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. 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.

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 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 IRB, IEC, 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 study 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.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant 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 participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. 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.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

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

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

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

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

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study 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 or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible,

contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

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

10.2 Appendix 2: Clinical Laboratory Tests

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted within 7 days prior to the first dose of study intervention in Cycle 1, and within 7 days prior to study intervention administration on Day 1 of optional Cycles 2 and 3. If a urine test is positive or not evaluable, a serum test will be required.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- The laboratory tests detailed in Table 6 will be performed by the local laboratory.
- Protocol-specific laboratory requirements for inclusion or exclusion of participants for study entry are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Hemoglobin
	Hematocrit
	Platelet Count
	WBC count (total and differential)
Chemistry	Albumin
	ALP
	ALT/SGPT
	AST/SGOT
	Bicarbonate
	Calcium
	Chloride
	Creatinine
	Glucose
	Magnesium
	Potassium
	Sodium
	Total bilirubin
	Urea/BUN
Other Screening Tests	Urine β-hCG pregnancy test (as needed for WOCBP). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=β human chorionic gonadotropin; BUN=blood urea nitrogen; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=white blood cell; WOCBP=women of childbearing potential. Note: Results will be documented in the participant's chart.	

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing 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 an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

    - Grade 4: Life threatening consequences; urgent intervention indicated.

    - Grade 5: Death related to AE.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

    - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

    - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

    - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE 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 medical 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 product and the AE 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 AE:**

  - **Exposure:** Is there evidence that the participant 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 studies 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.

  - **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; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant 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 study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention 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.

- 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:

    - Participant 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 participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
    - For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, 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 AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not Applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

There are no contraception requirements for male participants.

Female Participants

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c,d] • Intrauterine hormone-releasing system (IUS)[c,e] • Intrauterine device (IUD) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly*.
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
• 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)
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c. Male condoms must be used in addition to the hormonal contraception. d. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. e. IUS is a progestin releasing IUD.

Notes:
- Periodic abstinence (calendar, sympothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
- If a contraceptive method listed above is restricted by local regulation/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. This test should be conducted within 7 days before the first dose of study intervention of Cycle 1 and within 7 days prior to study intervention administration on Day 1 of optional Cycles 2 and 3. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not Applicable

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Emetogenicity of Chemotherapeutic Agents and Regimens

MINIMALLY EMETOGENIC (<10% frequency of emesis in the absence of prophylaxis)	LOW EMETOGENICITY (10% to <30% frequency of emesis in the absence of prophylaxis)	MODERATLEY EMETOGENIC (30% to <90% frequency of emesis in the absence of prophylaxis)	HIGHLY EMETOGENIC (>90% frequency of emesis in the absence of prophylaxis)
Single-agent Regimens	**Single-agent Regimens**	**Single-agent Regimens**	**Single-agent Regimens**
Asparaginase (*E. coli*) IM ≤6000 IU/m^2/dose	Cyclophosphamide IV 500 mg/m^2/dose	Cyclophosphamide IV 1000 mg/m^2/dose	Asparaginase (*Erwinia*) IV ≥20 000 IU/m^2/dose
	Cyclophosphamide PO 2-3 mg/kg/dose	Cytarabine IV 75 mg/m^2/dose	Busulfan IV ≥0.8 mg/kg/dose
Asparaginase (*Erwinia*) IM ≤25 000 IU/m^2/dose	Dasatinib PO 60-120 mg/m^2/dose	Dactinomycin IV 10 µg/kg/dose	Busulfan PO ≥1 mg/kg/dose
	Erlotinib PO 35-150 mg/m^2/day	Doxorubicin IV 25 mg/m^2/dose	Carboplatin IV ≥175 mg/m^2/dose
Chlorambucil PO ≤0.2 mg/kg/day	Everolimus PO 0.8-9 mg/m^2/day	Gemtuzumab IV 3-9 mg/m^2/dose	Cisplatin IV ≥12 mg/m^2/dose
Doxorubicin IV 10 mg/m^2/dose	Gefitinib PO 150-500 mg/m^2/day	Imatinib PO >260 mg/m^2/day	Cyclophosphamide IV ≥1200 mg/m^2/dose
Liposomal doxorubicin IV ≤50 mg/m^2/dose	Imatinib PO 260 mg/m^2/day	Interferon alpha IV 15-30 million IU/m^2/day	Cytarabine IV ≥3g/m^2/day
	Mafosfamide IT 1-6.5 mg/dose	Ixabepilone IV 3-10 mg/m^2/dose	Dactinomycin IV ≥1.35 mg/m^2/dose
Mercaptopurine PO ≤4.2 mg/kg/dose	Melphalan PO 0.2 mg/kg/dose	Methotrexate IT	Doxorubicin IV ≥30 mg/m^2/dose
Methotrexate PO/SC ≤10 mg/m^2/dose	Mercaptopurine PO ≤4.2 mg/kg/dose	Methotrexate IV 5 g/m^2/dose	Idarubicin PO ≥30 mg/m^2/dose
Pracinostat PO 25-45 mg/m^2/dose	Methotrexate IV 38-83 mg/m^2/dose	Topotecan PO 0.4-2.3 mg/m^2/day	Melphalan IV
Vincristine IV ≤1.5 mg/m^2/dose	Mitoxantrone IV ≤33 mg/m^2/dose	**Multiple-agent Regimens**	Methotrexate IV ≥12 g/m^2/dose
Multiple-agent Regimens	Procarbazine PO 50-100 mg/m^2/day	Cytarabine IV 60 or 90 mg/m^2/dose + methotrexate IV 120 mg/m^2/dose	**Multiple-agent Regimens**
Cisplatin IA ≤60 mg/m^2/dose + doxorubicin IA ≤30 mg/m^2/dose	Ruxolitinib PO 15-21 mg/m^2/dose		Cyclophosphamide ≥600 mg/m^2/dose + dactinomycin ≥1mg/m^2/dose
	Selumetinib PO 20-30 mg/m^2/dose	Cytarabine IV 100 mg/m^2/dose + daunorubicin IV 45 mg/m^2/dose + etoposide IV 100 mg/m^2/dose + prednisolone PO + thioguanine PO 80 mg/m^2/dose	
Cisplatin IA ≤60 mg/m^2/dose + pirarubicin IA ≤30 mg/m^2/dose	Sorafenib PO 150-325 mg/m^2/dose		Cyclophosphamide ≥400 mg/m^2/dose + doxorubicin ≥40mg/m^2/dose
	Temozolomide PO 200 mg/m^2/dose		
Mercaptopurine PO ≤2.5 mg/kg/dose + methotrexate PO ≤0.1 mg/kg/day	**Multiple-agent Regimens**	Liposomal doxorubicin IV 20-50 mg/m^2/dose + topotecan PO 0.6 mg/m^2/day	Cytarabine IV ≥90 mg/m^2/dose + methotrexate IV ≥150 mg/m^2/dose
	Cytarabine IV 60 mg/m^2/dose + methotrexate IV 90 mg/m^2/dose		Cytarabine IV + Teniposide IV
HEC=highly emetogenic chemotherapy; IA=intra-arterial; IM=intramuscular; IT=intrathecal; IV=intravenous; PO=oral; SC=subcutaneous. Notes: • Emetogenicity of multiple-agent chemotherapy regimens is determined by the most HEC of the regimen unless there is evidence indicating otherwise. • Emetogenicity of multiple-day chemotherapy regimens is determined by the most HEC given each day. • When a chemotherapy is classified as HEC at a specific dose, all higher doses are also classified as HEC. • When a chemotherapy is classified as minimally emetogenic at a specific dose, all lower doses are also classified as minimally emetogenic. • If a planned chemotherapy agent/regimen is not in this table, the investigator is encouraged to discuss the emetogenic stratification with the Sponsor Clinical Director.			Dacarbazine IV ≥250 mg/m^2/dose + doxorubicin IV ≥60 mg/m^2/dose
			Dactinomycin IV 900 µg/m^2/dose + ifosfamide IV 3 g/m^2/dose
			Etoposide IV ≥60 mg/m^2/dose + ifosfamide IV ≥1.2 g/m^2/dose
			Etoposide IV ≥250 mg/m^2/dose + thiotepa IV ≥300 mg/m^2/dose

Source: [Paw Cho Sing, E., et al 2019]

10.9 Appendix 9: Lansky and Karnofsky Performance Status Scales

Score	Lansky Play-Performance Scale Definitions (Participants ≤16 years)	Karnofsky Performance Scale Definitions (Participants >16 years)
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

Source: [Peus, D., et al 2013] [Lansky, S. B., et al 1987]

10.10 Appendix 10: Approximate Blood Volumes Drawn by Study Visit and Sample Type

	Cycle 1	
Study Visit:	**Screening**	**Follow-Up/ Discontinuation**
Blood Parameter	***Approximate Blood Volume (mL)***	
Hematology	~0.5	~0.5
Chemistry	~0.6	~0.6
Expected Total Blood Volume (mL)	~1.1	~1.1

10.11 Appendix 11: ECI Reporting Guidance for Hypersensitivity and Anaphylactic Reactions

Hypersensitivity and/or anaphylactic reactions are ECIs that must be reported to the Sponsor within 24 hours of occurrence in all cycles.

Hypersensitivity and/or anaphylactic reactions are defined as:

- Hypersensitivity: The term hypersensitivity describes objectively reproducible symptoms and signs of allergic disease initiated by exposure to a defined stimulus at a dose tolerated by normal persons.

- Anaphylactic reaction: The term anaphylactic reaction is an umbrella term for a serious, life-threatening generalized or systemic hypersensitivity reaction that is rapid in onset.

The following data points are required for each hypersensitivity-related ECI and must be entered in the appropriate electronic case report forms (eCRFs) or text fields in the SAE/ECI section of the AE eCRF. Please refer to the Data Entry Guidelines for specific instructions on hypersensitivity-related data entry requirements. If the answer to the question is not known or not applicable to the event, indicate that it is not known and comment if additional information is pending or it is not applicable (N/A).

- Timing of ECI symptoms relative to infusion

- Pre-medications

- Respiratory, skin, oropharyngeal, gastrointestinal, or cardiovascular signs and symptoms

- Pre-infusion vital signs and post-infusion vital signs

- Rescue treatments administered (ie, antihistamines, epinephrine, corticosteroids, oxygen, airway management, intubation, hemodynamic support)

- Whether intervention was discontinued, or, if continued, whether symptoms recurred after subsequent administration

- Whether the investigator classified the reaction as anaphylaxis or anaphylactoid

- If applicable, include alternative explanations for the hypersensitivity event, such as food allergy (eg, if a child is under the care of an allergist and had a known food allergy confirmed by positive food challenge or specific IgE test). Note the timing of the food allergen exposure relative to study intervention infusion and the onset of signs and symptoms of possible anaphylaxis.

10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
5-HT_3	5-hydroxytryptamine 3
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APaT	All Participants as Treated
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
CINV	chemotherapy-induced nausea and vomiting
C_{max}	maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	common terminology for adverse events
CTFG	Clinical Trial Facilitation Group
CYP3A4	cytochrome P450 3A4
DILI	drug-induced liver injury
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HEC	highly emetogenic chemotherapy
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhea method
MASCC	Multinational Association of Supportive Care in Cancer
MEC	moderately emetogenic chemotherapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	Non-Investigational Medicinal Product
NK_1	neurokinin-1
NSAE	nonserious adverse event

Abbreviation	Expanded Term
PK	pharmacokinetic
POGO	Pediatric Oncology Group of Ontario
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	schedule of activities
SOC	system organ class
sSAP	supplementary Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

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Supplemental Statistical Analysis Plan (sSAP)

Protocol Title: A Phase 4, Open-label, Single Arm Study to Evaluate the Safety and Tolerability of a Three-day Fosaprepitant Regimen Administered for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Participants Receiving Emetogenic Chemotherapy.

TABLE OF CONTENTS

LIST OF TABLES

1. INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2. SUMMARY OF CHANGES

Date	Page	Changes
27AUG2020	7	Added PDLC definition
27AUG2020	5	Added summary table and listing for COVID-19 related events

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below. The comprehensive plan is provided in Sections 3.2 – Responsibility for Analyses/In-House Blinding to 3.12 – Extent of Exposure.

Study Design Overview	A Phase 4, Open-label, Single Arm Study to Evaluate the Safety and Tolerability of a Three-day Fosaprepitant Regimen Administered for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Participants Receiving Emetogenic Chemotherapy
Treatment Assignment	Single Arm, Unblinded, Open-label
Analysis Populations	Efficacy: Not applicable for this safety study Safety: All Participants as Treated (APaT)
Primary Endpoint	•AEs •Discontinuation due to AEs
Key Secondary Endpoints	There are no key secondary endpoints in this study.
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	Not applicable for this safety study.

Statistical Methods for Key Safety Analyses	This is a single treatment arm safety study. In Cycle 1, proportions will be displayed for AEs, SAE(s), drug-related AE(s), and AE(s) leading to discontinuation from study intervention, which occur during the fosaprepitant treatment period plus 14 days post last dose of study intervention. For optional Cycles 2 and 3, proportions will be displayed for SAE(s), drug-related AE(s), and AE(s) leading to discontinuation from study intervention which occur during the fosaprepitant treatment period plus 14 days post last dose of study intervention.
Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	No multiplicity adjustment is planned forfs this study.
Sample Size and Power	The planned sample size is 100 participants.

3.2 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 and optional Cycles 2 and 3 of this study are being conducted as a non-randomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treated.

Results from all 3 cycles of chemotherapy will be presented in the CSR.

3.3 HYPOTHESES/ESTIMATION

There will be no hypotheses for this safety study.

3.4 ANALYSIS ENDPOINTS

This is a safety study; therefore, efficacy data will not be collected. Safety data will be evaluated in all cycles.

3.4.1 Safety Endpoints

Safety endpoints in Cycle 1 will be assessed by evaluation of all clinical and laboratory AEs including those that are considered drug-related, serious, serious drug-related, lead to discontinuation of study intervention, or other reportable safety events.

Safety endpoints in Cycle 2 and 3 will be assessed by evaluation of all SAEs, drug-related AEs, AEs that lead to discontinuation of study intervention, and other reportable safety events.

Safety and tolerability will also include assessment of additional study parameters including vital signs, physical examination, ECGs, and laboratory safety tests.

3.5 SAFETY ANALYSIS POPULATIONS

Safety analyses will be conducted in the APaT population, which consists of all allocated participants who received at least one dose of study treatment.

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

3.6 STATISTICAL METHODS

Additional data summaries and listings to account for potential COVID-19 impact are provided in Appendix 4.1.

3.6.1 Statistical Methods for Efficacy Analyses

There will be no efficacy analyses in this study.

3.6.2 Statistical Methods for Safety Analyses

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

The broad clinical and laboratory AE categories consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE which is both serious and drug-related, or who discontinued due to an AE will be summarized with descriptive statistics. AEs (specific as well as System Organ Class [SOC]) and continuing measures such as changes from baseline in laboratory, vital signs, and ECG parameters, will be provided in table format (Table 1).

Table 1 Analysis Strategy for Safety Parameters

Safety Endpoint	Descriptive Statistics
Any AE	X
Any Serious AE	X
Any Drug-Related AE	X
Any Serious and Drug-Related AE	X
Discontinuation due to AE	X
Discontinuation due to a Drug-Related AE	X
Specific AEs, SOCs	X
Change from Baseline Results (Labs, ECGs, Vital Signs)	X

AE = adverse event, SOC = system organ class, X = results will be provided

The following predefined limits of change in Table 2 will be assessed.

Table 2 Predefined Limits of Change

Laboratory Test	Criteria
Hematocrit	Decrease ≥20% and value <LLN Increase ≥20% and value >ULN
WBC	Decrease ≥20% and value <LLN Increase ≥20% and value >ULN
Platelet	Decrease ≥25% and value <LLN Increase ≥50% and value >ULN
Bilirubin	Increase ≥100% and value >ULN Increase ≥50% and value >1.5x ULN Increase ≥50% and value >2x ULN Increase ≥50% and value >3x ULN Increase ≥50% and value >5x ULN
AST	Increase ≥100% and value >ULN Increase ≥50% and value >1.5x ULN Increase ≥50% and value >2x ULN Increase ≥50% and value >3x ULN Increase ≥50% and value >5x ULN
ALT	Increase ≥100% and value >ULN Increase ≥50% and value >1.5x ULN Increase ≥50% and value >2x ULN Increase ≥50% and value >3x ULN Increase ≥50% and value >5x ULN
Neutrophil	Decrease ≥20% and value <LLN Increase ≥20% and value >ULN
BUN	Increase ≥50% Increase ≥20% and value BLN >ULN
Serum creatinine	Increase ≥50% Increase ≥20% and value BLN >ULN

[†]Increases and decreases are relative to baseline.
ALT = alanine aminotransferase; AST = aspartate aminotransferase;
BLN = baseline; BUN = blood urea nitrogen; LLN = Lower limit of normal range; ULN = Upper limit of normal range; WBC = white blood cell.

3.6.3 Demographics and Baseline Characteristics

For each relevant demographic and baseline characteristic, descriptive statistics 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 participants screened, allocated, the primary reasons for screening failure, and primary reasons for discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical table.

3.7 INTERIM ANALYSES

No interim analyses are planned for this study.

3.8 MULTIPLICITY

No multiplicity adjustment is planned since no hypothesis testing will be conducted in this study.

3.9 SAMPLE SIZE AND POWER CALCULATIONS

The planned sample size is 100 participants. With a sample size of 100 participants, if the underlying incidence rate is 1% then the probability of observing ≥1 AE is 0.63; furthermore, if the underlying incidence rate is 5% then the probability of observing ≥1 AE is 0.99.

3.10 SUBGROUP ANALYSES

All results will be displayed by the 4 age groups (6 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to 17 years).

3.11 COMPLIANCE (MEDICATION ADHERENCE)

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

3.12 EXTENT OF EXPOSURE

The extent of exposure (dose and duration) to fosaprepitant will be summarized by the number of participants exposed to fosaprepitant for defined periods of time.

4. APPENDICES

4.1 Additional analyses accounting for possible COVID-19 impact

In order to assess the impact of COVID-19, the following listings and summaries will be provided in the CSR as follows:

- The Summary table of PDs Associated with COVID-19
- The corresponding listing

The COVID-19 PD listings will include information in terms of impact (WHAT was impacted, HOW was it impacted and WHEN was it impacted) will be saved in the Deviations Cumulative Report (DCR) prior to Database Lock (DBL).