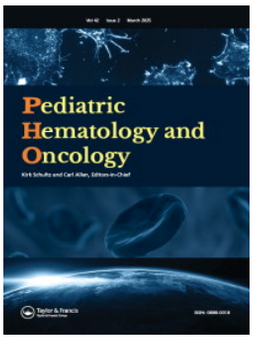

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Safety and Tolerability of a 3-Day Fosaprepitant Regimen for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients: Results of an Open-Label, Single-Arm Phase 4 Trial

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ABSTRACT

Convenient multiday dosing of antiemetic regimens for the prevention of chemotherapy-induced nausea and vomiting (CINV) are needed in pediatric patients, who are more likely than adults to be treated with emetogenic chemotherapy over multiple consecutive days. Intravenous (IV) fosaprepitant is approved for the prevention of CINV in children aged 6 months and older. This open-label, single-arm study assessed the safety and tolerability of a 3-day fosaprepitant regimen (consecutive daily IV administration on days 1–3) plus a serotonin receptor antagonist with or without dexamethasone in pediatric patients (6 months to 17 years) receiving emetogenic chemotherapy. Study treatment was initiated at the start of a chemotherapy cycle (cycle 1); patients completing cycle 1 could participate in optional cycles 2 and 3. Primary endpoints included adverse events (AEs) and AE-related discontinuation during cycle 1.98/100. Patients completed cycle 1; 69 participated in optional cycles 2 and 3. The AE profile during cycle 1 was typical of cancer patients receiving emetogenic chemotherapy; 80/100 (80.0%) patients experienced ≥1 AE. AE rates were generally similar between patients aged 6 months to <2 years (11/15 patients [73.3%]), 2 to <6 years (22/30 [73.3%]), 6 to <12 years (24/25 [96.0%]), and 12–17 years (23/30 [76.7%]). Rates of drug-related AEs (4/100 [4.0%]) and AE-related discontinuations (2/100 [2.0%]) were low. Similar trends in safety outcomes were observed during cycles 2 and 3. No deaths were reported. The 3-day IV fosaprepitant regimen for the prevention of CINV was generally well tolerated in pediatric patients receiving emetogenic chemotherapy.

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Introduction

Despite the development of contemporary antiemetic agents, chemotherapy-induced nausea and vomiting (CINV) continues to be one of the most distressing side effects of chemotherapy in the pediatric setting,[1–3] with symptoms occurring in up to 70%

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of children.[4,5] In 2017, Pediatric Oncology Group of Ontario (POGO) management guidelines for pediatric patients receiving highly emetogenic chemotherapy (HEC) recommended a three-drug combination of a serotonin (5-HT_3) receptor antagonist (granisetron, ondansetron, or palonosetron), dexamethasone, and the oral neurokinin 1 receptor antagonist (NK_1RA) aprepitant.[6] Two-drug combinations of a 5-HT_3 antagonist and dexamethasone can be used if the NK_1RA is contraindicated, or palonosetron and the NK_1RA aprepitant if dexamethasone is contraindicated;[6] single-agent prophylaxis with palonosetron is also recommended if dexamethasone is contraindicated.[6] Guideline recommendations for pediatric patients scheduled to receive moderately emetogenic chemotherapy (MEC) include a two-drug combination of a 5-HT_3 antagonist (granisetron, ondansetron, or palonosetron) and dexamethasone or, if dexamethasone is contraindicated, a 5-HT_3 antagonist with the NK_1RA aprepitant;[6] single-agent prophylaxis with a 5-HT_3 antagonist is also recommended if dexamethasone is contraindicated.[6] Recent guideline updates by the American Society of Oncology (2020) and POGO (2022) added fosaprepitant as an NK_1RA option to regimens recommended for use in pediatric patients scheduled to receive HEC or MEC.[7,8]

The NK_1RA fosaprepitant is a water-soluble prodrug of aprepitant that is converted to aprepitant following intravenous (IV) administration. Its biologic effects are attributable to aprepitant,[9] and bioequivalence has been demonstrated in adults for single oral doses of aprepitant 125 mg and 165 mg and IV fosaprepitant 115 mg and 150 mg, respectively.[10,11] In the pediatric setting, the use of IV fosaprepitant is supported by evidence from well-controlled studies in adult patients[12,13] and additional safety, efficacy, and pharmacokinetic data in pediatric patients up to 17 years of age; these studies primarily evaluated a single dose regimen of fosaprepitant.[14] The efficacy and safety of fosaprepitant was also supported by data from a well-controlled study of a 3-day oral aprepitant regimen in pediatric patients aged 6 months to 17 years.[15] As a result, the efficacy of a 1-day IV fosaprepitant regimen in pediatric patients can be extrapolated from prior IV data for the 1-day fosaprepitant regimen in adult patients.[16,17] In both the United States and European Union (EU), a three-drug combination of fosaprepitant, a 5-HT_3 antagonist, and dexamethasone has been approved for the pediatric population as a 1-day regimen or a 3-day regimen (IV fosaprepitant administered on 3 consecutive days or interchangeably with oral aprepitant on days 2 and 3).[17,18]

A 3-day IV fosaprepitant regimen may be an important antiemetic treatment option for the pediatric population, given that children are more likely to be treated with emetogenic chemotherapy over multiple consecutive days. Furthermore, some patients may not be able to tolerate oral dosing of antiemetics (ie, due to nausea, vomiting), and there is inherent difficulty in administering oral medications to children.[19,20] Therefore, IV administration of afosaprepitant regimen for 3 consecutive days may provide convenient dosing and improved adherence.

In adult patients receiving MEC or HEC, a single-dose IV fosaprepitant regimen has been previously shown to be generally well tolerated, with the most frequently reported adverse events (AEs) being fatigue, diarrhea, constipation, asthenia, neutropenia, vomiting, anorexia, nausea, hiccups, headache, decreased appetite, and alopecia.[12,13] Infusion-site reactions were also reported in these studies, which included pain, irritation, thrombophlebitis, erythema, pruritus, and induration.[12,13] In the pediatric setting, the safety profile of IV fosaprepitant is considered to be similar to that of

adult patients receiving a single-dose IV fosaprepitant regimen; common AEs included anemia, neutropenia, thrombocytopenia, and febrile neutropenia.[14,18] To date, clinical data on a 3-day IV fosaprepitant regimen in the pediatric setting are largely limited to extrapolation from IV data of single-dose fosaprepitant in both adult and pediatric patients. Therefore, the present study was conducted to collect additional clinical 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 in pediatric patients who were scheduled to receive either MEC or HEC.

Methods

Study design and patient population

Study PN045 was a phase 4, non-randomized, single-arm, multicenter, open-label study of a 3-day fosaprepitant regimen for the prevention of CINV in pediatric patients with cancer aged 6 months to 17 years. Patients were enrolled from 25 centers across nine countries (Greece, Hungary, Lithuania, Netherlands, Peru, Poland, Russia, United Kingdom, and United States), most of which were hospital and medical centers, with one non-hospital clinical research site (NCT04054193). The primary phase of the study comprised a screening phase, a 3-day intervention period initiated at the start of a chemotherapy cycle (cycle 1), and a 14-day follow-up phase (Figure 1). Patients who completed cycle 1 were then invited to participate in up to 2 additional optional cycles (cycles 2 and 3)in which the 3-day fosaprepitant regimen was administered as in cycle 1 and additional assessment of safety was undertaken. Cycles 2 and 3 had to be completed within 3 months from the end of cycle 1.

Key inclusion criteria for participation in cycle 1 included the following: age 6 months to 17 years; documented malignancy; scheduled receipt of chemotherapeutic agents with moderate (30% to <90% frequency of emesis in the absence of prophylaxis) or high (>90%) risk of emetogenicity[21] (or a chemotherapy agent not previously tolerated due to vomiting); Lansky Play Performance score ≥60 (aged ≤16 years)or Karnofsky performance status score ≥60 (aged >16 years); a preexisting functioning central venous catheter for study drug administration; life expectancy ≥3 months; and bodyweight ≥6 kg. Previous treatment with chemotherapy was allowed. Patients who completed the preceding study chemotherapy cycle with no unresolved drug-related AEs were also eligible to participate in the optional cycles 2 and 3. Patients were excluded from the study if they had previously received fosaprepitant, were scheduled to receive stem-cell rescue therapy, had evidence of alcohol abuse or dependence, were pregnant, had active infection, or had abnormal hematologic, hepatic, or renal laboratory values.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved the institutional review board of each participating center (Supporting Information Table S1). Written informed consent was obtained from the patient and/or his/her parent or guardian before study entry.

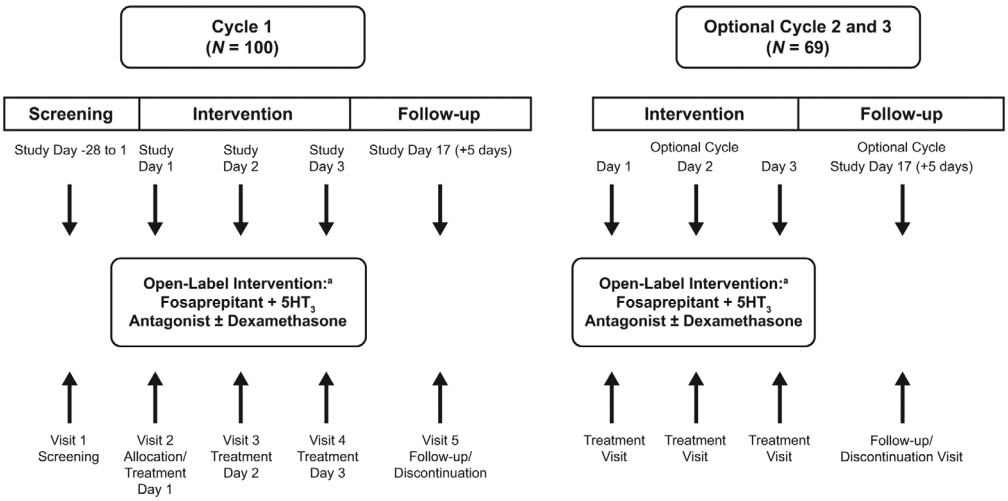

Figure 1. Study design. 5-HT_3, serotonin receptor antagonist. [a]Patients received an open-label, 3-day IV fosaprepitant regimen comprising fosaprepitant + a 5-HT_3 receptor antagonist with or without dexamethasone. On day 1, patients receivedan IV infusion of fosaprepitant 115 mg (aged 12–17 years) or 3 mg/kg (aged 6 months to <12 years; not exceeding 115 mg) and a 5-HT_3 receptor antagonist chosen at the discretion of the investigator and administered according to the product label or local standard of care. On days 2 and 3, patients received IV infusions of fosaprepitant 80 mg (aged 12–17 years) or 2 mg/kg (aged 6 months to <12 years; not exceeding 80 mg). Dexamethasone could be administered as part of the fosaprepitant regimen at the investigator's discretion. The dose of dexamethasone was reduced to 50% of the usual prescribed dose on each day of concomitant administration with fosaprepitant and for 24 hours following the last dose of fosaprepitant (ie, dose reduction required on days 1–4).

Treatment regimen

All eligible patients received an open-label, 3-day regimen of fosaprepitant administered *via* a central venous catheter with a concomitant 5-HT_3 antagonist; dexamethasone use was permitted at the investigator's discretion (Figure 1). Dosing of fosaprepitant was as follows: single-dose IV fosaprepitant 3 mg/kg up to 115 mg for patients aged 6 months to <12 years, or 115-mg fixed dose for those aged 12–17 years on day 1 of emetogenic chemotherapy; and single-dose IV fosaprepitant 2 mg/kg up to 80 mg for patients aged 6 months to <12 years, or 80-mg fixed dose for those aged 12–17 years on days 2 and 3. A 5-HT_3 antagonist was required on day 1 of the fosaprepitant regimen, but was optional on days 2 and 3, administered at the discretion of the investigator. Patients were stratified by age on day 1 of chemotherapy cycle 1 (6 months to <2 years, 2 to <6 years, 6 to <12 years, or 12–17 years) and emetogenic potential of the planned emetogenic chemotherapy in cycle 1 (HEC or MEC).

Study end points and assessments

The primary endpoints of this study were AEs (non-serious AEs and serious AEs [SAEs]) and AEs leading to discontinuation during cycle 1 in the overall study population.

Safety and tolerability were assessed by the evaluation of AEs during cycle 1 and optional cycles 2 and 3 (Supplemental Methods). An AE was defined as any untoward medical occurrence in a patient who received at least one dose of study treatment, regardless of suspected relationship to treatment, or any worsening of a preexisting condition that was temporally associated with study medication administration. SAEs were defined as any untoward medical occurrence that was life threatening; was a congenital anomaly/birth defect in the offspring of trial participants; or resulted in hospitalization, significant disability/incapacity, or death. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).[22] All hypersensitivity events were independently evaluated by the Sponsor and investigators to determine whether they met Sampson criteria for anaphylaxis.[23] Additional safety assessments included the following: clinical safety laboratory assessments during all cycles (hematology [eg, hemoglobin, hematocrit], chemistry [eg, creatinine, total bilirubin], and pregnancy testing); routine laboratory assessments during cycle 1 only (hematology and chemistry); vital signs during all cycles (ie, blood pressure, heart rate, respiratory rate, and temperature); full/directed physical examination during cycle 1 only; and 12-lead electrocardiography during cycle 1 only (Supplemental Methods).

During cycle 1, all AEs (SAEs and non-serious AEs) were recorded from the screening phase through 14 days after the last treatment dose. In optional cycles 2 and 3, all SAEs, non-serious AEs related to fosaprepitant (drug-related AEs [AEs thought by the investigator to be associated with treatment with fosaprepitant]), and AEs leading to discontinuation were reported from completion of cycle 1 through 14 days following treatment in the last cycle.

Statistical analyses

The planned sample size of this study was 100 patients. Although no formal calculations of study power were performed, it was determined that the probability of observing at least one AE with the selected sample size of 100 was 0.63 if the underlying incidence rate was 1% and was 0.99 if the underlying incidence rate was 5%.

Safety was analyzed in the all-patients-as-treated (APaT) population, which comprised all allocated patients who received at least one dose of study treatment. Descriptive statistics were used to summarize baseline characteristics and AEs for the APaT population. Proportions of AEs, SAEs, drug-related AEs, and AEs leading to discontinuation were reported and compared between stratified age categories (6 months to <2 years; 2 to <6 years; 6 to <12 years; and 12–17 years). Treatment compliance was calculated as the percentage of total fosaprepitant volume prepared that was infused in a patient based on study day, age, and weight (if applicable). No formal statistical testing was performed, and adjustment for multiplicity was not conducted for this study.

Results

Baseline characteristics and disposition

The first patient was screened on September 9, 2019, and patient recruitment closed on November 4, 2020. Of the 115 screened patients, 103 were enrolled into the study

Table 1. Baseline characteristics (all-patients-as-treated population).

Characteristic	All patients ($N = 100$)
Age, mean ± *SD*, years	7.59 ± 5.03
Age distribution, *n* (%)	
6 months to <2 years	15 (15.0)
2 to <6 years	30 (30.0)
6 to <12 years	25 (25.0)
12–17 years	30 (30.0)
Male, *n* (%)	51 (51.0)
Race, *n* (%)	
White	78 (78.0)
American Indian or Alaska Native	14 (14.0)
Black or African American	2 (2.0)
Multiple	6 (6.0)
Ethnicity, *n* (%)	
Not Hispanic or Latino	74 (74.0)
Hispanic or Latino	22 (22.0)
Emetogenic potential of chemotherapy in cycle 1, *n* (%)	
Highly emetogenic	75 (75.0)
Moderately emetogenic	25 (25.0)

and 100 received at least one dose of the study treatment and were included in the APaT population (Supporting Information Figure S1). In total, 98/100 (98%) patients completed cycle 1 and 2/100 (2%) patients discontinued (1 due to physician decision and 1 because of withdrawal by parent/guardian). Following cycle 1, 69 patients participated in optional cycles 2 and 3, with 48/69 patients (69.6%) completing both optional cycles 2 and 3, and 21/69 (30.4%) patients discontinuing (2 due to physician decision; 2 because of withdrawal by parent/guardian; 17 due to other reasons). A total of 28 patients elected not to participate in optional cycles 2 and 3 (eight because of withdrawal by parent/guardian; one because of withdrawal by patient; 19 due to other reasons). Treatment compliance was 98.3%in cycle 1 and 100%in cycles 2 and 3.

Baseline characteristics are summarized in Table 1. The overall median (range) age was 7.0 (0.6–17.0) years, 51.0% were male, and most were white (78.0%). Most patients received HEC during cycle 1 (75.0%); the remaining 25.0% received MEC. The most frequently used concomitant HEC agent was cisplatin in both cycle 1 (24.0%) and optional cycles 2 and 3 (24.6%) (Supporting Information Table S2). The most frequently used concomitant MEC agents included ifosfamide (35.0%), doxorubicin (31.0%) and cyclophosphamide (27.0%) in cycle 1, and ifosfamide (36.2%), doxorubicin (30.4%), and cyclophosphamide (29.0%) in optional cycles 2 and 3 (Supporting Information Table S2).

Adverse events during cycle 1

In the overall study population, ≥1 AE was reported in 80 of 100 patients (80.0%), SAEs were reported in 30 of 100 patients (30.0%), and AEs leading to discontinuation were reported in 2 of 100 patients (2.0%) (Table 2). When stratified by age category, ≥1 AE was reported in 11/15 patients (73.3%) aged 6 months to <2 years, 22/30 (73.3%) of those aged 2 to <6 years, 24/25 (96.0%) of those aged 6 to <12 years, and 23/30 (76.7%) of those aged 12–17 years. Although the number of patients reporting AEs was slightly higher in the 6 to <12 years age group, there was no pattern related to

Table 2. Summary of adverse events in patients treated with the fosaprepitant regimen during cycle 1 (all-patients-as-treated population; $N = 100$).

	Number of patients (%)	
AEs		
Any	80 (80.0)	
Drug-related	4 (4.0)	
Serious AEs		
Any	30 (30.0)	
Drug-related	1 (1.0)	
Discontinuation due to an AE		
Any	2 (2.0)	
Drug-related	1 (1.0)	
Death	0 (0)	
AEs occurring in ≥5% of patients	NCI CTCAE Grade 1 or 2	NCI CTCAE Grade 3 or 4
≥1 AE	31 (31.0)	49 (49.0)
Anemia	6 (6.0)	19 (19.0)
Nausea	25 (25.0)	0 (0)
Febrile neutropenia	1 (1.0)	20 (20.0)
Vomiting	16 (16.0)	0 (0)
Neutropenia	0 (0)	15 (15.0)
Neutrophil count decreased	1 (1.0)	13 (13.0)
Thrombocytopenia	4 (4.0)	7 (7.0)
Hematotoxicity	9 (9.0)	1 (1.0)
Platelet count decreased	3 (3.0)	6 (6.0)
WBC decreased	2 (2.0)	5 (5.0)
Decreased appetite	6 (6.0)	1 (1.0)
Constipation	6 (6.0)	0 (0)
Pyrexia	5 (5.0)	1 (1.0)
Leukopenia	0 (0)	5 (5.0)
Fatigue	4 (4.0)	1 (1.0)

AE, adverse event; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; WBC, white blood cell.

specific AEs. SAEs were reported in 3/15 patients (20.0%) aged 6 months to <2 years, 9/30 (30.0%) of those aged 2 to <6 years, 10/25 (40.0%) of those aged 6 to <12 years, and 8/30 (26.7%) of those aged 12–17 years. AEs leading to discontinuation were low during cycle 1, occurring in 2/30 patients (6.7%) aged 12–17 years (anaphylactoid reaction and infusion-related reaction); no discontinuations were reported in the other age categories. No deaths were reported in any age category during cycle 1.

The AE profile during cycle 1 is summarized in Table 2. The most frequently reported AEs (≥5% of patients) were from the blood and lymphatic system disorders system organ class (SOC; anemia, febrile neutropenia, neutropenia, thrombocytopenia, and hematotoxicity), the gastrointestinal disorders SOC (nausea and vomiting), and the investigations SOC (decreased neutrophil count). No cases of neurotoxicity were reported. AEs were Grade 1 or 2 in 31 of 100 patients (31.0%) and Grade 3 or 4 in 49 of 100 patients (49.0%).

Overall, the incidence of drug-related AEs was low in cycle 1, occurring in 4 of 100 (4.0%) patients (Table 2) and composed of nausea, anaphylactoid reaction, infusion-related reaction, dizziness, and headache ($n = 1$ each). When stratified by age category, drug-related AEs were reported in 0/13patients aged 6 months to <2 years, 0/30 patients aged 2 to <6 years, 1/25 patients (4.0%) aged 6 to <12 years, and 3/30 (10.0%) of those aged 12–17 years. These AEs included nausea, anaphylactoid reaction, infusion-related reaction, dizziness, and headache ($n = 1$ each). One drug-related AE was considered a serious event. This was an infusion-related reaction reported in a

patient in the 12–17 years age category, which resulted in discontinuation of the study treatment.

Laboratory findings, hepatic safety, and hypersensitivity reactions

No unexpected laboratory findings were observed, with the most common laboratory abnormalities being decreases in hematologic measurements, including white blood cell count, neutrophil count, hemoglobin, and platelet count (Supporting Information Tables S3).

The most frequently reported liver function findings were alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN; 9.1%), aspartate aminotransferase (AST) ≥3 × ULN (6.0%), and aminotransferase (ALT or AST) ≥3 × ULN (10.1%). No cases of drug-induced liver injury (defined as ALT or AST ≥3 × ULN, total bilirubin ≥2 × ULN, and alkaline phosphatase <2 × ULN at the same time) were reported during cycle 1.

Seven hypersensitivity events were reported. Of these, 2events reported in cycle 1 were considered to be related to fosaprepitant and led to discontinuation of the study treatment. One patient had a serious AE of infusion-related reaction that led to discontinuation of fosaprepitant mid-infusion. This event was classified as anaphylaxis by the Sponsor, but not the investigator. One patient who received concomitant anthracycline-based chemotherapy (doxorubicin) experienced a non-serious AE of anaphylactoid reaction with periorbital and facial edema as well as vomiting. This event was classified as anaphylactoid by both the Sponsor and investigator. Both patients recovered without sequelae. The remaining five hypersensitivity events were not considered related to fosaprepitant and were not classified as anaphylactic or anaphylactoid. These included one case of possible Stevens-Johnson syndrome (type IV hypersensitivity reaction; cycle 2) that was considered by the investigator to be related to other concomitant therapies (ie, trimethoprim/sulfamethoxazole and/or methotrexate), one case of non-serious wheezing (cycle 1), one case of non-serious urticaria (cycle 1), and two cases of non-serious pruritus (one case each in cycles 1 and 2).

Adverse events during optional cycles 2 and 3

In the overall study population, ≥1 AE was reported in 46 of 69 patients (66.7%) and SAEs were reported in 27 of 69 patients (39.1%). When stratified by age category, ≥1 AE was reported in 5/9 patients (55.6%) aged 6 months to <2 years, 14/24 (58.3%) of those aged 2 to <6 years, 16/17 (94.1%) of those aged 6 to <12 years, and 11/19 (57.9%) of those aged 12–17 years. SAEs were reported in 3/9 patients (33.3%) aged 6 months to <2 years, 8/24 (33.3%) of those aged 2 to <6 years, 9/17 (52.9%) of those aged 6 to <12 years, and 7/19 (36.8%) of those aged 12–17 years. No cases of AEs leading to discontinuation of study treatment, or deaths were reported in any age category during optional cycles 2 and 3.

The AE profile during optional cycles 2 and 3 is summarized in Supporting Information Table S4. The most frequently reported AEs (≥5% of patients) were from the blood and lymphatic system disorders SOC (anemia, febrile neutropenia, and hematotoxicity) and the gastrointestinal disorders SOC (nausea and vomiting). No cases of neurotoxicity were reported. AEs were Grade 1 or 2 in 12 of 69 patients (17.4%) and Grade 3 or 4 in 34 of 69 patients (49.2%).

Overall, the incidence of drug-related AEs in optional cycles 2 and 3 was also low, occurring in 2/69 patients (2.9%); both of these patients were in the 6 to <12 years age category (2/17 [11.8%]). These included 1 case each of vomiting and somnolence. No cases of serious drug-related AEs were reported in any age category during optional cycles 2 and 3.

Laboratory findings, hepatic safety, and overdose

Similar to cycle 1, most laboratory abnormalities were decreases in hematologic measurements, including white blood cell count, neutrophil count, platelet count, and hemoglobin.

Routine laboratory samples were not collected for patients participating in optional cycles 2 and 3. However, no cases of drug-induced liver injury were reported. An accidental fosaprepitant overdose of 1.5 mg on day 33 and 1 mg on days 34 and 35 was reported in a patient during optional cycle 2, which did not result in an AE; the accidental overdose was considered resolved on day 35.

Discussion

In the current single-arm study, a 3-day IV fosaprepitant regimen administered concomitantly with a 5-HT_3 receptor antagonist (with or without dexamethasone) was generally well tolerated in pediatric patients receiving emetogenic chemotherapy. Although the lack of a control or placebo arm in this study limited the ability to determine relative changes in the incidence of AEs related to the 3-day IV fosaprepitant regimen, safety and tolerability profiles for this regimen were generally similar between age categories and considered typical of a population of patients with cancer receiving emetogenic chemotherapy. In previously published aprepitant and fosaprepitant studies in pediatric patients, the most frequently reported AEs (≥4%) included leukopenia, anorexia, anemia, febrile neutropenia, diarrhea, elevated serum liver enzymes (AST, ALT), constipation, fever, headache, thrombocytopenia, mucositis, vomiting, abdominal pain; rates of drug-related AEs and infusion-site reactions were low and no deaths were reported.[14,24–27] No new or unexpected safety signals were observed in this study, and drug-related AE rates were low in both cycle 1 and optional cycles 2 and 3, highlighting that safety is maintained over multiple cycles.

The most commonly reported AEs were hematologic (ie, febrile neutropenia [21.0%], anemia [25.0%]) or gastrointestinal (nausea [25.0%], vomiting [16.0%]) in nature. The incidences of these AEs were generally similar to those observed in the treatment arm of prior placebo-controlled trials of fosaprepitant. Incidence rates of febrile neutropenia in cycle 1 (21.0%) and optional cycles 2 and 3 (21.7%) in the current study were similar to rates reported in the combination standard antiemetic therapy plus NK_1RA arms of previous placebo-controlled studies (20%–25%) among adult or adolescent patients, which were higher than incidence rates of febrile neutropenia in the control arms (standard antiemetic therapy alone).[28,29] However, previous placebo-controlled studies did not report increased rates of febrile neutropenia for antiemesis regimens with a NK_1RA, irrespective of patient age.[13,15,24,30–34] Furthermore, although ifosfamide-induced neurotoxicity may be associated with the concomitant use of

aprepitant or fosaprepitant, no cases of neurotoxicity were reported in the current study despite the frequent use of concomitant ifosfamide.[35]

Infusion-related AEs have been previously reported to be a limiting factor for fosaprepitant administration.[36] Furthermore, fosaprepitant contains a synthetic surfactant, polysorbate 80, which is associated with a number of safety issues, including hypersensitivity reactions,[37,38] and infusion-related reactions may also be exacerbated when fosaprepitant is administered during anthracycline-based chemotherapy.[39–41] Hypersensitivity events were infrequent (7/100 patients) in the current study, which included 2 drug-related AEs reported in cycle 1 that resulted in discontinuation of study treatment. These drug-related events comprised a patient receiving concomitant anthracycline-based chemotherapy (doxorubicin) who had a non-serious AE of anaphylactoid reaction with periorbital and facial edema as well as vomiting, and another patient with a serious AE of infusion-related reaction. Both patients recovered without sequelae.

This study has a few limitations. Due to the single-arm design of this study, comparisons between the 3-day IV fosaprepitant regimen and a control arm to determine relative changes in safety and tolerability were not possible. In addition, although no unexpected safety signals were observed across the age groups assessed, sample sizes within each age category were small (30 or fewer in each age category). Finally, the generalizability of the safety data from this study may be impacted by inclusion of a predominantly white (78%) study population and the fact that all patients received fosaprepitant *via* a central venous catheter.

In conclusion, use of a 3-day IV fosaprepitant regimen for the prevention of CINV in pediatric patients receiving emetogenic chemotherapy was generally well tolerated. In addition, the safety profile of this regimen was generally similar across the age groups assessed. These findings further support use of a 3-day IV fosaprepitant regimen as a convenient multiday IV antiemetic treatment option for pediatric patients.

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Author contributions

CD, ASA, and RY were involved in the conception, design or planning of the study, analysis of the data, and interpretation of the results. JLGL was involved in the acquisition and analysis of the data and interpretation of the results. All authors were involved in the drafting of the manuscript and critically reviewing or revising the manuscript for important intellectual content. All authors approved the final version of the manuscript prior to submission.

Disclosure statement

CD, RY, and ASA are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and own shares/stocks/stock options at Merck & Co., Inc., Rahway, NJ, USA. JLGL declares no conflict of interest.

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Data availability statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing Website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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