Original Article

A Phase 3, randomized, double-blind study of single-dose fosaprepitant for prevention of cisplatin-induced nausea and vomiting: Results of an Indian population subanalysis

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Abstract

CONTEXT: Currently, there is limited data on the prevention of chemotherapy-induced nausea and vomiting (CINV) in Indian patients. **AIMS:** This *post hoc* study assessed the efficacy and safety of fosaprepitant compared with aprepitant for prevention of CINV in the Indian population. A subgroup analysis was performed from data collected in a phase 3 study of intravenous (IV) fosaprepitant or oral aprepitant, plus the 5-HT_3 antagonist ondansetron and the corticosteroid dexamethasone, in cisplatin-naïve patients with solid malignancies. **MATERIALS AND METHODS:** Patients scheduled to receive cisplatin ($\geq$70 mg/m^2) were administered a single IV dose of fosaprepitant dimeglumine (150 mg) on day 1 or a 3-day dosing regimen of oral aprepitant (day 1:125 mg, days 2 and 3:80 mg) with standard doses of ondansetron and dexamethasone. Patients recorded nausea and/or vomiting episodes and their use of rescue medication and were monitored for adverse events (AEs) and tolerability. **STATISTICAL ANALYSIS USED:** Differences in response rates between fosaprepitant and aprepitant were calculated using the Miettinen and Nurminen method. **RESULTS:** In the Indian subpopulation (n = 372), efficacy was similar for patients in both the fosaprepitant or aprepitant groups; complete response in the overall, acute, and delayed phases and no vomiting in all phases were approximately 4 percentage points higher in the fosaprepitant group compared with the aprepitant group. Fosaprepitant was generally well-tolerated; common AEs were similar to oral aprepitant. **CONCLUSIONS:** IV fosaprepitant is as safe and effective as oral aprepitant in the Indian subpopulation and offers an alternative to the oral formulation.

Key Words: Antiemetic therapy, aprepitant, chemotherapy-induced nausea and vomiting, fosaprepitant, Indian population, noninferiority

Introduction

Despite significant progress in the management of nausea and vomiting associated with chemotherapy, these side effects continue to limit the effectiveness of cancer therapy and reduce patient quality of life. Prophylactic treatment has been shown to significantly reduce the risk of nausea and vomiting in both initial and repeat courses of highly emetogenic (eg, cisplatin, high-dose anthracyclines) or moderately emetogenic (eg., lower-dose anthracyclines, carboplatin) chemotherapy regimens.[1] The risk period for nausea and vomiting can be divided into 2 phases, an acute period of risk within 24 hours of chemotherapy administration and a delayed period of risk occurring more than 24 h after administration. High-dose cisplatin (>50 mg/m^2) is associated both with severe acute emesis in nearly all patients in the absence of antiemetic prophylaxis, and with delayed emesis in 57% to 89% of patients.[2] Results from several clinical studies have demonstrated that addition of a neurokinin-1 receptor antagonist (NK1RA) to a standard 5-hydroxytryptamine (5-HT_3) receptor antagonist and dexamethasone antiemetic regimen improved the prevention of chemotherapy-induced nausea and vomiting (CINV) throughout the overall period of risk (0-120 hours following initiation of chemotherapy). The added benefit of an NK1RA was seen in patients receiving highly or moderately emetogenic chemotherapy, both for the first time and over multiple cycles.[2-6]

The NK1RA fosaprepitant is a water-soluble phosphorylated prodrug that is rapidly converted to the antiemetic aprepitant.[7,8] Fosaprepitant dimeglumine

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(EMEND for injection, IV EMEND) is approved in a number of countries worldwide at a dose of 115 mg, as an alternative to 125 mg oral aprepitant, on day 1 of a 3-day regimen (with oral aprepitant administered on days 2 and 3).[9] Fosaprepitant dimeglumine is also approved as a single dose (150 mg) on day 1, as an alternative to the standard 3-day oral aprepitant regimen. Single-dose intravenous (IV) fosaprepitant on day 1 was shown to be noninferior to a 3-day regimen of oral aprepitant in patients receiving highly emetogenic chemotherapy (high-dose cisplatin) for the first time, providing an important prophylactic option in patients who cannot tolerate oral medication due to anticipatory emesis, stomatitis, or other contraindications.[7]

To date, there are limited data on the risk of CINV and the efficacy and tolerability of antiemetic therapy in the Indian population. A Singapore survey study examining risk factors for CINV among head and neck cancer patients receiving high-dose cisplatin, showed increased anxiety and history of CINV to be significant predictors of CINV occurrence.[10] Several studies conducted in other Asian populations (that is, Chinese and Japanese) have demonstrated that the addition of aprepitant to a 5-HT_3 antagonist and dexamethasone regimen reduces the incidence of CINV in both the highly and moderately emetogenic settings.[11,12] In a study conducted in Indian cancer patients receiving high-dose cisplatin, ondansetron was demonstrated to be more efficacious than the combination of metoclopramide and dexamethasone for prevention of CINV.[13] Taking advantage of the relatively large patient population enrolled at sites in India in the pivotal noninferiority trial reported by Grunberg *et al*.,[7] our paper reports results of a *post hoc* analysis evaluating the efficacy and safety of fosaprepitant compared with aprepitant for the prevention of CINV in the Indian subpopulation of patients in the large phase 3 trial.

Materials and Methods

This was a randomized, double-blind, parallel-group study of IV fosaprepitant or oral aprepitant plus the 5-HT_3 antagonist ondansetron and the corticosteroid dexamethasone in cisplatin-naïve men and women with histologically confirmed solid malignancies.[7] Patients receiving cisplatin at a dose of at least 70 mg/m^2 for the first time received a single IV dose of 150 mg fosaprepitant dimeglumine on day 1 or a 3-day dosing regimen of oral aprepitant (125 mg on day 1, 80 mg on days 2 and 3). The dexamethasone regimen consisted of 12 mg orally on day 1 and 8 mg orally on days 2 to 4 for patients receiving the oral aprepitant regimen, or 12 mg orally on day 1, 8 mg orally on day 2, and 8 mg twice a day orally on day 3 or 4 for patients receiving the single-dose IV fosaprepitant regimen. Ondansetron was administered as a 32-mg IV dose on day 1 only. Both treatment groups were allowed rescue therapy for nausea and vomiting. This international trial enrolled patients from 5 regions, including North America, South America, Europe, Asia-Pacific, and Africa. The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with International Conference on Harmonisation, Good Clinical Practices, and all applicable regulatory guidelines.

Patients enrolled in the study must have been scheduled to receive their first course of cisplatin (≥70 mg/m^2) for documented solid malignancies, have had a Karnofsky performance score of at least 60, and have had a predicted life expectancy of at least 3 months. Premenopausal female patients of reproductive potential must have demonstrated a negative urine pregnancy test and agreed to use a double-barrier form of contraception at least 14 days prior to and throughout the study, and for at least 1 month following the last dose of study medication. Patients must have been able to read, understand, and complete a study diary and questionnaire; understand study procedures; and, give written informed consent. Exclusion criteria included symptomatic primary or metastatic central nervous system (CNS) malignancy, radiation therapy to the abdomen/pelvis in the week prior to treatment, stem cell rescue therapy with cisplatin, vomiting less than 25 hours prior to treatment day 1, and treatment with multiple-day chemotherapy with cisplatin in single-cycle or moderate/high emetogenic chemotherapy (<6 days prior to and/or during the 6 days following cisplatin infusion). Patients were also excluded if they had active infection or uncontrolled disease; had a history of any illness that might confound the results of the study or pose unwarranted risk in administering the study drug to the patient; had a history of illicit drug use or alcohol abuse; had a mental incapacitation or emotional or psychiatric disorder; had a history of hypersensitivity to aprepitant, ondansetron, or dexamethasone; were breast-feeding; participated in an aprepitant/investigational drug study within 4 weeks of treatment day 1; had a concurrent medication condition that would preclude administration of dexamethasone for 4 days; had received systemic corticosteroid therapy; or, had abnormal laboratory values.

Patients recorded the time and date of nausea and/or vomiting episodes and their use of rescue medication in a diary during the first 120 hours after initiation of chemotherapy. A vomiting episode was defined as one or more distinct episodes of emesis (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach

contents). Distinct episodes were defined as those separated by at least 1 minute. Patients assessed daily nausea using a visual analog scale. Rescue medication was to be taken only to relieve established nausea or vomiting, not for prevention.

The primary efficacy end point of the phase 3 trial was to evaluate the noninferiority of fosaprepitant compared with aprepitant for complete response, defined as no vomiting and no use of rescue therapy, during the overall phase (120 hours following initiation of cisplatin therapy). Secondary end points included assessment of the proportion of patients with complete response in the delayed phase (25-120 hours following initiation of cisplatin therapy) and the proportion of patients with no vomiting overall. Complete response and no vomiting in the acute phase (0-24 hours following initiation of cisplatin chemotherapy) and the use of rescue medications were exploratory efficacy end points in the study.

The safety and tolerability of fosaprepitant was also evaluated in the phase 3 trial. Patients were monitored for adverse events (AEs) and tolerability at all visits. In addition to the reporting of subjective events during study drug therapy and for 14 days post therapy, standard prestudy and poststudy measurements (including medical history, physical exam, and 12-lead electrocardiogram [prestudy only]) and laboratory tests (including hematology, chemistry, urinalysis, and pregnancy tests for females of child-bearing age) were collected. Events related to the primary end point (vomiting, retching, nausea) were not defined as AEs during the period of data collection with the diary–day 1 until the morning of day 6–unless they met the definition of a serious AE. Severe infusion site pain, severe infusion site erythema, and/or severe infusion site induration, as well as any episode of infusion site thrombophlebitis, were designated events of clinical interest. All AEs were analysed using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events v3.0.

For the primary efficacy analysis, a total of 1113 evaluable patients per regimen were expected to yield 90% power to declare noninferiority for the single-dose fosaprepitant dimeglumine regimen, using a noninferiority margin of –7.0 percentage points (pp), assuming a 2-sided 5% significance level and an expected response rate of 67.7% in each treatment regimen. Noninferiority margins were predefined for secondary end points as –7.3 pp for complete response during the delayed phase and –8.2 pp for no vomiting in the overall phase. For noninferiority testing, if the lower bound of the calculated 95% confidence interval (CI) was greater than the predefined margin, the fosaprepitant was declared noninferior to aprepitant for that end point; noninferiority was not determined for the Indian subpopulation, since the initial statistical boundaries were established for the overall population. The Miettinen and Nurminen method (stratified for gender) was used for calculation of the difference and 95% CI for the difference in response rates between fosaprepitant and aprepitant. The efficacy analysis populations included patients who received at least one dose of study therapy, received cisplatin chemotherapy, and had at least one posttreatment efficacy assessment.

Results

A total of 2322 patients were enrolled in the study, prestratified by gender and randomized to treatment; 2247 patients (1109 receiving fosaprepitant, 1138 receiving aprepitant) were considered evaluable for efficacy. The overall study population was approximately 56% white, 26% Asian, 3% American Indian or Native Alaskan, 2% black, 0.1% Native Hawaiian or Pacific Islander, and 13% multiracial. Three hundred seventy-two patients were enrolled at study sites in India and constitute the patient subgroup for the *post hoc* analysis; 100% of the Indian subpopulation was classified as Asian.

Baseline characteristics were similar in the fosaprepitant and aprepitant treatment groups in both the overall study population and the Indian subpopulation [Table 1]. The median age was slightly lower in the Indian subpopulation (51 years for the fosaprepitant arm and 50 years for the aprepitant arm) than in the overall trial population (56 years for the fosaprepitant arm and 57 years for the aprepitant arm), and the percentage of males enrolled was somewhat higher (75.3% for the fosaprepitant arm and 72.6% for the aprepitant arm) than in the overall trial population (62.9% for the fosaprepitant arm and 63.7% for the aprepitant arm). The frequency of cancer types was different in the Indian subpopulation than in the overall trial population, with a reduced frequency of lung cancer and a higher rate of gastrointestinal (GI) and miscellaneous cancers. In addition, GI cancers were more common in the aprepitant arm than in the fosaprepitant arm in the Indian subpopulation.

Assessment of the Indian subpopulation demonstrated that a slightly greater percentage of patients in the fosaprepitant treatment group achieved complete responses in the overall phase (77.1% [95% CI: 70.2, 83.1]) compared with the aprepitant group (73.4% [95% CI: 66.4, 79.6]; difference: 3.5 pp [95% CI: –5.5, 12.4]) [Figure 1]. In the delayed phase, 77.7% (95% CI: 70.8, 83.6) of patients in the fosaprepitant group reported a complete response compared with 73.9% (95% CI: 66.9, 80.1) in the

Table 1: Baseline patient and disease characteristics as seen in the study

Characteristic	Overall population		Indian subpopulation	
	IV fosaprepitant (*n*=1147)	Oral aprepitant (*n*=1175)	IV fosaprepitant (*n*=182)	Oral aprepitant (*n*=190)
Median age, y (range)	56.0 (19-86)	57.0 (19-82)	51.0 (23-75)	50.0 (19-79)
Sex, %				
Men	62.9	63.7	75.3	72.6
Women	37.1	36.3	24.7	27.4
Race, %				
American Indian, Native Alaskan	2.8	2.8	N/A	N/A
Asian[a]	25.8	26.0	100	100
Black	1.8	1.9	N/A	N/A
Multiracial	13.0	13.4	N/A	N/A
Native Hawaiian, Pacific Islander	0.1	0.2	N/A	N/A
White	56.5	55.7	N/A	N/A
History of motion sickness, %	0.0	0.3	0.0	1.1
History of vomiting during pregnancy,[b] %	0.3	0.3	0.0	0.0
Type of malignancy, %				
Lung cancer	46.2	47.5	29.1	26.8
Gastrointestinal cancer	21.9	21.0	36.3	43.7
Reproductive or genitourinary cancer	15.0	15.1	9.3	13.2
Miscellaneous or site unspecified	7.2	5.7	12.1	8.4
Renal and urinary tract cancer	4.3	3.5	6.0	3.2
Breast cancer	2.9	2.2	3.3	2.1
Lymphoma	0.9	1.1	1.6	1.1
Hepatic and biliary cancer	0.7	1.4	1.1	0.5
Endocrine cancer	0.1	0.9	0.0	0.5
Nervous system cancer	0.1	0.1	0.0	0.0

[a]Patients from Asia Pacific were enrolled from Hong Kong, India, New Zealand, and Korea. All patients enrolled in India are categorized as Asian; there are no specific demographic data for patients enrolled in Indian sites. [b]Only female patients were considered for vomiting during pregnancy. IV=Intravenous; N/A=Not applicable

aprepitant group (difference: 3.5 pp [95% CI: –5.3, 12.4]). Similarly, in the overall phase, a slightly greater percentage of the Indian subpopulation patients in the fosaprepitant group reported no vomiting (77.1% [95% CI: 70.2, 83.1]) compared with the aprepitant group (73.4% [95% CI: 66.4, 79.6]; difference: 3.5 pp [95% CI: –5.5, 12.4]) [Figure 2]. In the Indian subpopulation, similar differences were observed in the acute phase for complete response and in both the acute and delayed phases for no vomiting (approximately 3-4 pp greater in the fosaprepitant group compared with the aprepitant group) [Figures 1 and 2]. For the overall population, similar percentages of patients achieved complete responses and reported no vomiting in the overall, acute, and delayed phases in both the fosaprepitant and aprepitant treatment groups [Figures 1 and 2].

In the Indian subpopulation, 92.0% (95% CI: 86.9, 95.6) of patients in the fosaprepitant group reported no use of rescue medication in the overall phase compared with 89.7% (95% CI: 84.3, 93.7) in the aprepitant group (difference: 2.2 pp [95% CI: –3.9, 8.5]) [Figure 3]. No significant differences in the use of rescue medication were observed in either the acute phase or delayed phase between the 2 treatment groups within the Indian subpopulation. These results are similar to those observed for the overall study population, in which similar percentages of patients reported no use of rescue medication in the overall, acute, and delayed phases in both the fosaprepitant and the aprepitant treatment groups [Figure 3].

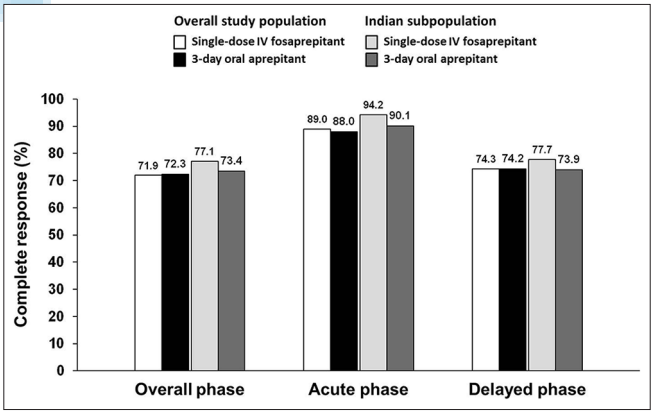

Figure 1: Patients with complete response following treatment with fosaprepitant compared with aprepitant. IV = intravenous

Results from the overall study population determined that IV fosaprepitant is noninferior to the oral aprepitant regimen based on the lower bound of 95% CI for the difference in response rate: overall phase complete response was –4.1 pp, which was lower than the prespecified value of –7.0 pp. The full efficacy and noninferiority analyses of the IV fosaprepitant regimen versus oral aprepitant for the overall phase 3 study population were published by Grunberg *et al*.,[7] In the Indian subpopulation, the AE profile of specified clinical events for the IV fosaprepitant 150-mg regimen was generally similar to the 3-day oral aprepitant regimen [Table 2]. The incidence of asthenia (8.8% vs. 13.2%), dehydration (4.4% vs. 8.4%), and hyponatremia (1.6% vs. 5.8%) was lower in patients treated with fosaprepitant compared with aprepitant. On the other hand, constipation (17.6% vs. 10.0%) was reported by more patients treated with fosaprepitant compared with aprepitant. The safety results are similar to the overall study population; the safety profile for the fosaprepitant 150-mg regimen was generally consistent with that of the 3-day aprepitant regimen [Table 2]. The incidence of urinary tract infections (1.0% vs 0.3%) was higher in patients treated with fosaprepitant compared with aprepitant; there was also a slight increase in the incidence of hypertension (1.5% vs 0.6%). The incidence of asthenia (8.6% vs. 11.6%) and anorexia (6.6% vs. 9.1%) was lower in patients treated with fosaprepitant compared with aprepitant.

Reactions at the site of fosaprepitant or placebo infusion were predefined as events of clinical interest. None of the patients in the Indian subpopulation experienced infusion-related reactions. In the overall study population, no cases of severe erythema or induration were reported. There were 16 cases (1.4%) of infusion site pain in the fosaprepitant group (14 grade 1/2 and 2 grade 3 events) and 1 (0.1%) in the aprepitant group. There were 2 cases of severe infusion site pain in the fosaprepitant group and none in the aprepitant group (difference did not reach statistical significance). Although rare, there were significantly more cases of presumed infusion-associated thrombophlebitis in the fosaprepitant group (n = 9, 0.8%) compared with the aprepitant group (n = 1, 0.1%). A full analysis of the safety profile of the IV fosaprepitant regimen, compared with orally administered aprepitant in the overall study population, was previously published with the efficacy analysis of the overall study population.[7]

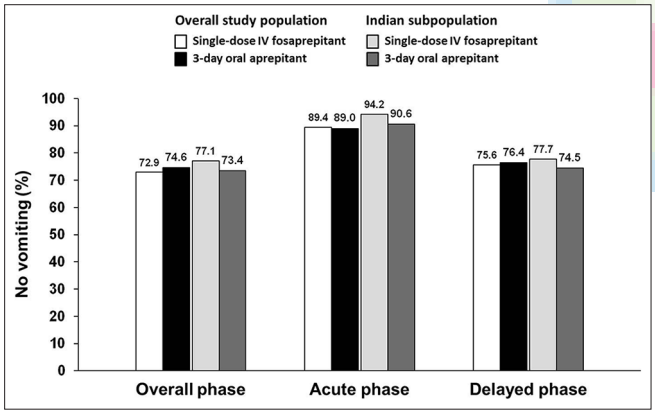

Figure 2: Patients with no vomiting following treatment with fosaprepitant compared with aprepitant. IV = Intravenous

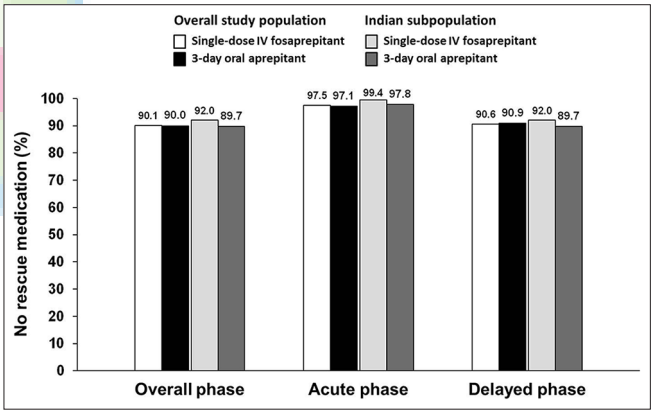

Figure 3: Patients not requiring the use of rescue medication following treatment with fosaprepitant compared with aprepitant IV = Intravenous

Table 2: Most common adverse events reported by ≥5% of patients in any treatment group in the Indian subpopulation as seen in the study*

Adverse event	Overall patients, *n* (%)		Indian patients, *n* (%)	
	IV fosaprepitant (*n*=1143)	Oral aprepitant (*n*=1169)	IV fosaprepitant (*n*=182)	Oral aprepitant (*n*=190)
Constipation	121 (10.6)	112 (9.6)	32 (17.6)	19 (10.0)
Asthenia	98 (8.6)	136 (11.6)	16 (8.8)	25 (13.2)
Diarrhoea	89 (7.8)	102 (8.7)	26 (14.3)	31 (16.3)
Vomiting	75 (6.6)	65 (5.6)	12 (6.6)	11 (5.8)
Abdominal pain	34 (3.0)	42 (3.6)	13 (7.1)	12 (6.3)
Dehydration	32 (2.8)	41 (3.5)	8 (4.4)	16 (8.4)
Hyponatremia	15 (1.3)	15 (1.3)	3 (1.6)	11 (5.8)

*Data for overall study population provided for comparison. IV=Intravenous

Discussion

Little is known about the risk of CINV and the efficacy of antiemetic treatments in Indian or Asian patients. In a recent longitudinal, prospective, observational study, breast cancer patients in Malaysia of 3 different races (Malay, Chinese, and Indian) were monitored for CINV within the first 24 hours and after 3 to 5 days of chemotherapy treatment.[14] All patients received prophylactic granisetron and dexamethasone, and metoclopramide and dexamethasone as post medication. Results showed that a larger percentage of Chinese patients than Malay or Indian patients suffered from acute and/or delayed nausea. In a Singapore survey study that examined risk factors for CINV among patients with head and neck cancer receiving high-dose cisplatin, increased anxiety and history of CINV were shown to be significant predictors of CINV occurrence, while previously identified risk factors of history of motion sickness and alcohol use were not found to correlate with CINV. Such findings suggest that the risk of CINV may potentially vary by race and ethnicity. Therefore, it is important to ensure that CINV risk evaluation and prevention be optimized for all patients, including the Indian population.

Most large, randomized, controlled studies examining antiemetic regimens for prevention of CINV have not enrolled substantial numbers of Asian patients or have not reported results by race or ethnicity. However, several studies conducted in Asian populations have demonstrated that the addition of aprepitant to a 5-HT_3 antagonist and dexamethasone regimen reduces the incidence of CINV in both the highly and moderately emetogenic chemotherapy regimens, consistent with data from trials that enrolled patients of multiple races.[11,12] A study conducted in Indian cancer patients receiving high-dose cisplatin demonstrated that the 5-HT_3 antagonist ondansetron is more efficacious than the combination of metoclopramide and dexamethasone for prevention of CINV.[13] The goal of the *post hoc* study described here was to determine if the efficacy and safety findings for single-dose IV fosaprepitant versus 3-day oral aprepitant as part of a triple regimen for the prevention of CINV were comparable between the overall trial population and the Indian subpopulation.

Results from the overall trial population demonstrated that the triple antiemetic regimen including a single 150-mg dose of IV fosaprepitant on day 1 is noninferior to a triple antiemetic regimen using oral aprepitant administered over 3 days for the prevention of CINV in patients receiving a first course of highly emetogenic, high-dose cisplatin.[7] The primary end point, the rate of complete response throughout the overall period of risk, was found to be no different for patients receiving single-dose IV fosaprepitant and patients receiving a 3-day oral aprepitant regimen. In addition, the rate of complete response in the delayed period and the rate of vomiting in the overall period were also the same between the 1-day IV fosaprepitant and 3-day oral aprepitant regimens. For the Indian subpopulation of 372 patients, efficacy appears to be similar for patients receiving the single-dose IV fosaprepitant regimen and the 3-day oral aprepitant regimen. In the fosaprepitant group, there was approximately a 4 pp higher rate of complete response in the overall, acute, and delayed phases, as well as approximately a 4 pp higher rate of no vomiting in all phases, compared with the aprepitant group. The differences could not be analysed statistically, as this was a *post hoc* analysis. These data indicate that the noninferiority of the 1-day IV fosaprepitant regimen to the standard 3-day oral aprepitant regimen seems to hold for both a large, racially diverse population in the pivotal phase 3 trial and for a subset of Indian patients.

In the Indian subpopulation, IV fosaprepitant was generally well tolerated, and common AEs were similar to those with the oral aprepitant regimen. The incidence of constipation was slightly increased in patients receiving IV fosaprepitant, while the frequency of asthenia, dehydration, and hyponatremia was slightly higher in patients receiving oral aprepitant. The safety experience in the Indian subpopulation was similar to that in the overall study population, where IV fosaprepitant was generally well tolerated in patients receiving highly emetogenic chemotherapy, with an AE profile similar to that of oral aprepitant.[7] Urinary tract infections were slightly more common in patients receiving IV fosaprepitant in the overall study population, while asthenia and anorexia were slightly more common in patients receiving oral aprepitant. With the exception of infusion-associated thrombophlebitis (<1% of patients in each treatment group), there were no significant differences between regimens in the incidence of events of clinical interest in the overall population.

In summary, the equivalence of these regimens, as demonstrated in the phase 3 study, allows for a more convenient administration of an NK1 receptor antagonist for the prevention of CINV[7] and appears to be efficacious among patients of multiple races, including Indian patients. Therefore, single-dose IV fosaprepitant may provide a useful alternative to the 3-day regimen of oral aprepitant, and as a single-day regimen, IV fosaprepitant may improve patient compliance with antiemetic therapy.

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