Three palonosetron regimens to prevent CINV in myeloma patients receiving multiple-day high-dose melphalan and hematopoietic stem cell transplantation


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Background: Explore safety and efficacy of three palonosetron-containing regimens for emesis prevention over 7 days in multiple myeloma (MM) patients receiving melphalan (100 mg/m²) and hematopoietic stem cell transplantation (HSCT).

Patients and methods: Randomized, double-blind pilot study in MM patients (n = 73) receiving 1, 2, or 3 days of 0.25 mg palonosetron (30-s i.v. bolus) 30 min before melphalan (days –2 and –1) and HSCT (day 0). Patients received dexamethasone (20 mg i.v., days –2 and –1) immediately before or after study drug/placebo. Daily diaries recorded emesis, rescue medication, nausea duration, and adverse events (AEs).

Results: Seven-day complete protection (no emesis) occurred in 41.7% [95% confidence interval (CI) 22.1% to 63.4%], 41.7% (95% CI 22.1% to 63.4%), and 44.0% (95% CI 24.2% to 65.1%) of patients receiving 1, 2, or 3 days of palonosetron, respectively (P = 0.43). Complete response (emesis free without rescue medication) occurred in 8.3%, 20.8%, and 20.0% (P = 0.14). Common AEs (‡10%) were mild-to-moderate diarrhea, constipation, headache, insomnia, and flatulence. No serious AEs occurred.

Conclusions: Palonosetron with dexamethasone was safe and effective in preventing emesis in MM patients receiving melphalan and HSCT. This pilot study with a limited number of patients suggests that multiple doses of palonosetron could be more effective than a single dose in making patients emesis free without need for rescue medication. However, even multiple doses of palonosetron resulted in only 20% of patients being emesis free without rescue medication, suggesting that further improvement will require development of more effective combination antiemetic therapy.

Key words: high-dose melphalan, myeloma, nausea, palonosetron

Introduction

Multiple myeloma (MM) accounts for slightly >10% of all hematologic cancers [1] and is characterized by the clonal expansion of neoplastic plasma cells within the bone marrow, elevated serum immunoglobulin, and osteolytic bone disease [2]. High-dose multiple-day melphalan is a commonly used conditioning regimen for patients with MM who are undergoing hematopoietic stem cell transplantation (HSCT) [3] but is often associated with difficult-to-control nausea and vomiting [4–6].

Current guidelines do not address prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving preparative regimens for HSCT [7]. The Multinational Association of Supportive Care in Cancer recommends that standard therapy for such situations is with a serotonin [5-hydroxytryptamine-3 (5HT3)] receptor antagonist and dexamethasone [8]. This practice prevents emesis on the first day of chemotherapy for many patients, but control on subsequent days is limited [8, 9]. Moreover, current regimens for preventing CINV are relatively ineffective in patients undergoing multiple-day moderate-to-highly emetogenic chemotherapy such as melphalan or other high-dose chemotherapy with HSCT [4, 5, 8, 9]. Standard antiemetic therapy with ondansetron and dexamethasone has demonstrated emesis prevention rates from 4% to 20%, nausea prevention rates of ~5%, and the need for rescue antiemetics in >95% of patients over a 4- to 7-day course of high-dose chemotherapy [4, 5, 8]. The limited effectiveness of existing regimens indicates that new approaches are

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needed to improve emesis and nausea prevention in this setting [9, 10].

Palonosetron [Aloxi® (USA), Onicit® (global)] is a 5HT3 receptor antagonist that, unlike first-generation 5HT3 receptor antagonists, exhibits allosteric receptor binding with positive cooperativity (i.e. binding affinity increases with additional receptor occupancy) [11]. Additionally, palonosetron has been shown to have a high binding affinity for the serotonin receptor and to trigger internalization of cell surface serotonin receptor sites and has a long half-life [11–13].

Generally, one dose of i.v. palonosetron has proven sufficient to protect against emesis and nausea in many patients receiving various single-dose chemotherapy regimens [14–17] as well as for some multiple-day chemotherapy regimens [18–20]. Although a retrospective study reported that palonosetron was effective if given with dexamethasone in transplant recipients [21], clinical data related to protection from highly emetogenic therapies used to treat MM patients are limited. The difficult-to-control emesis and nausea associated with multiple-day conditioning regimens preceding HSCT [4]—and the HSCT itself [22]—tend to worsen over the course of treatment [5] and thus would be expected to require protection for longer durations. Another retrospective study found that MM patients receiving one i.v. bolus dose of 0.25 mg palonosetron before HSCT required fewer doses of rescue medication in the 6 subsequent days than those who received a single i.v. bolus dose of 24 mg ondansetron with dexamethasone [23]. The present prospective pilot study was designed to evaluate single- and multiple-day administration schedules of palonosetron and begin to identify the optimal emesis prevention regimen for MM patients undergoing conditioning chemotherapy and HSCT.

patients and methods

study objectives, design, and drug administration

The primary objective of this double-blind, randomized pilot study was to explore the efficacy and safety of three administration schedules of i.v. palonosetron 0.25 mg for preventing emesis and nausea in MM patients receiving melphalan (100 mg/m²) for 2 days (days −2 and −1) before HSCT (day 0). Patients were assigned to one of three cohorts (Figure 1) receiving i.v. palonosetron as 30-s i.v. bolus infusions −30 min before melphalan and HSCT on day −2 (cohort 1), days −2 and −1 (cohort 2), or days −2, −1, and 0 (cohort 3); infusions of saline were given as placebo in cohorts 1 and 2. Dexamethasone (20 mg i.v.) was administered to all patients on days −2 and −1 immediately before or after the study drugs.

Secondary objectives of the study were to assess the safety of the three different schedules of palonosetron, their ability to prevent nausea and reduce nausea severity and duration, and their impact on activities of daily living due to emesis and nausea. Exploratory analyses were carried out to detect trends in the rate of complete protection (CP) from emesis over 7 days with increasing number of palonosetron doses, as well as for daily efficacy measures.

The study protocol and consent forms were approved by the institutional review board at each participating center, and all enrolled patients provided written informed consent before participation.

patient inclusion/exclusion criteria

Patients eligible to participate were ≥18 years, had histologically confirmed MM, a Karnofsky index ≥50%, and were scheduled to receive a melphalan-containing conditioning regimen (100 mg/m² on days −2 and −1) followed by autologous HSCT on day 0. Women of childbearing potential were required to use reliable contraceptive measures and have a negative pregnancy test at screening. Patients were excluded if they experienced any vomiting, retching, or grade 2–4 nausea (as defined by the National Cancer Institute—Common Terminology Criteria for Adverse Events, version 3.0) in the 24 h preceding chemotherapy, had ongoing vomiting from any organic etiology, were scheduled to receive any emetogenic chemotherapeutic agents during the study other than those specified in the protocol, or were scheduled to undergo radiotherapy of the upper abdomen or cranium or total body irradiation within 1 week before or during the study. Also excluded were patients with any known contraindication to 5HT3 receptor antagonists, who had received any investigational drugs within 30 days before study entry or drugs with potential antiemetic efficacy within 24 h before the start of chemotherapy on day −2, or who were unable to understand or unwilling to cooperate with study procedures.

Figure 1. Study description. Study design, patient allocation, treatments, and schema for major study-related procedures. Palonosetron 0.25 mg i.v. was given for 1, 2, or 3 doses on the days shown. Study drugs [palonosetron or placebo (O)] were delivered 30 min before melphalan chemotherapy (days −2 and −1) or before HSCT (day 0). Dexamethasone 20 mg i.v. was administered on days −2 and −1 immediately before or after study drugs. *Screening and baseline procedures were carried out from Days −16 to −2.
study procedures

Screening and baseline procedures were carried out from days −16 to −2. The schedule of treatments and other study-related procedures, including administration of the Osoba Nausea and Emesis Module, a brief five-item questionnaire [24], were outlined in Figure 1. Patients or nurses recorded information about emetic episodes, use of rescue medication, adverse events (AEs), and the severity and duration of nausea in a daily diary on days −2 to +4. On day +5, physical examinations and clinical laboratory tests were carried out, vital signs were recorded, and the final Osoba questionnaire was completed.

efficacy assessments

Emesis prevention was measured daily over the 7-day study interval starting with initiation of melphalan on day −2 and ending on day +4 after HSCT. The occurrence and number of emetic episodes, use of rescue medication, and nausea severity (as measured on a 4-point Likert scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe) recorded in patient diaries were the data sources for efficacy assessments. Nausea duration was recorded every 6 h and evaluated by tallying the number of hours at each severity level. The Osoba questionnaire, administered on days −2, 0, and +5, assessed interference from nausea or emesis on appetite, sleep, physical activities, social life, and enjoyment of life, using a 4-point scale (1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much).

Safety of the palonosetron regimens was assessed by evaluating the occurrence of AEs, recorded on a daily basis, as well as changes in vital signs and clinical laboratory tests from baseline to study completion.

data analysis

study populations. The intent-to-treat (ITT) population included all patients randomly assigned to a treatment cohort and was the basis for all efficacy analyses. The safety population consisted of all patients randomly assigned to a treatment cohort who received at least one dose of palonosetron and was identical to the ITT population.

statistical analyses of efficacy and safety end points. Descriptive statistics were used to summarize demographic and baseline patient characteristics and all other statistical analyses were exploratory in nature. The primary efficacy end point was the CP rate, defined as the proportion of patients with no emetic episodes throughout the cumulative 7-day study period (days −2 through +4). A descriptive summary of the CP rate as the primary end point (i.e. % of patients with no emesis) was used to assess the efficacy of each palonosetron regimen. Antiemetic regimens in patients with hematologic malignancies receiving high-dose chemotherapy with melphalan before HSCT have been associated with CP rates on the order of 15%–20% [4, 5]; thus, a CP rate of 35% with a 95% confidence interval (CI) lower bound >15% was considered clinically meaningful and indicative of efficacy. For this pilot study, a sample size of 25 patients per group was estimated to be sufficient to determine the actual CP rate within ±19% with 95% CI. Patients with partial or completely missing diary data for CP were considered as not having protection or needing rescue medications during the time periods for calculation of proportions and CIs.

Secondary end points to assess efficacy included the proportion of patients who, over the 7-day study period, (i) required no rescue medication, (ii) achieved complete response (CR; defined as no emesis and no use of rescue medication), and (iii) had no nausea over the 7-day study period. Missing data were handled as above. Additionally, the total numbers of hours that patients experienced mild, moderate, severe, or any nausea were determined, and Osoba questionnaire results were analyzed to assess the impact of nausea/emesis on patient functioning.

For the primary end point of CP, exploratory analyses to test for an increasing linear trend in response with increasing number of palonosetron doses were carried out using the exact one-sided Jonckheere–Terpstra trend test [25]. For the primary and secondary end points, descriptive summaries of data collected on a daily basis for each treatment group were provided. No corrections for multiple comparisons were made due to the exploratory nature of the study.

To assess the safety of each palonosetron regimen, the incidences of treatment-emergent AEs, as well as investigator attribution of relationship to study medication, were summarized using descriptive analyses. Clinically significant differences in vital signs or laboratory data were also evaluated using descriptive analyses.

results

patients

Seventy-three patients who were randomized to the 1-day (n = 24), 2-day (n = 24), and 3-day (n = 25) palonosetron cohorts completed the study and comprised the ITT and safety populations. Two of 75 eligible patients were enrolled but not randomized and received no study drugs due to insufficient documentation of antiemetic dosing in the 24 h before day −2. Patient baseline characteristics, summarized in Table 1, were similar across treatment cohorts. Overall, the majority were male (64%) and Caucasian (75%); patients ranged in age from 32 to 72 years and in body weight from 48.7 to 131.8 kg. Most were non- or ex-smokers, the majority never or only rarely used alcohol, and less than one-third of the patients were chemotherapy naive before to study entry.

antiemetic efficacy of palonosetron-containing regimens

Over the 7-day course of the study, the CP (no emesis) rates were 41.7% (95% CI 22.1% to 63.4%), 41.7% (95% CI 22.1% to 63.4%), and 44.0% (95% CI 24.4% to 65.1%), respectively, for groups receiving 1-, 2-, or 3-day i.v. palonosetron (Figure 2). For the primary CP end point, the 1-, 2-, or 3-day palonosetron dosing cohorts were not statistically different from each other (P = 0.43). A significant trend toward increasing CP with additional doses of palonosetron was observed on day 0 of HSCT, when the proportion of patients achieving CP was 66.7%, 79.2%, and 92.0% for the 1-, 2-, and 3-day regimens, respectively (P = 0.015).

Secondary end points to assess the efficacy of the three palonosetron-containing regimens, including the proportion of patients per cohort who required no rescue medication, achieved CR (no emesis and no rescue medication) or had no nausea throughout the study are shown in Figure 3. Multiple days of palonosetron consistently resulted in better daily relief as reflected in the secondary emesis/nausea indicators. Over the entire 7 study days, however, linear trends in increased efficacy with increasing number of doses did not reach statistical significance.

Rescue antiemetics were not required in 8.3%, 33.3%, and 24.0% of patients receiving 1-, 2-, and 3-day palonosetron, respectively (P = 0.10; Figure 3A). On days +1 and +3, linear trends toward fewer patients requiring rescue medications with increasing number of palonosetron doses were significant (P < 0.05 and P < 0.005, respectively). Of note, a significant trend (P < 0.01) was detected on day −2 when all cohorts had received the same therapy (one i.v. dose each of palonosetron and...
dexamethasone). Over the 7-day course of the study, the proportion of patients achieving CR was 8.3%, 20.8%, and 20.0% with 1-, 2-, and 3-day palonosetron, respectively (P = 0.14; Figure 3B). Analogous to the no rescue medication measurements, linear trends favoring multiple palonosetron doses were significant on days −2 and +3 (both P < 0.05). Overall nausea prevention rates were 8.3%, 29.2%, and 16.0% throughout the 7-day study for patients receiving 1-, 2-, and 3-day palonosetron, respectively; again, the trend in increased efficacy with multiple doses was not statistically significant (P = 0.25; Figure 3C). On study days −1 and +4, the 2- and 3-day palonosetron cohorts experienced significantly better nausea

Table 1. Demographic and baseline characteristics of study patients

|                      | 1-day palonosetron (n = 24) | 2-day palonosetron (n = 24) | 3-day palonosetron (n = 25) | P value
|----------------------|-----------------------------|-----------------------------|-----------------------------|---------
| **Sex, n (%)**       |                             |                             |                             | 0.507   |
| Male                 | 13 (54.2)                   | 17 (70.8)                   | 17 (68.0)                   |         |
| Female               | 11 (45.8)                   | 7 (29.2)                    | 8 (32.0)                    |         |
| **Age (years)**      |                             |                             |                             | 0.890   |
| Mean (SD)            | 58.2 (8.38)                 | 57.9 (10.79)                | 59.3 (7.64)                 |         |
| Range                | 38–71                       | 32–70                       | 44–72                       |         |
| **Ethnicity, n (%)** |                             |                             |                             | 0.268   |
| White (Caucasian)    | 20 (83.3)                   | 17 (70.8)                   | 18 (72.0)                   |         |
| Black                | 3 (12.5)                    | 4 (16.7)                    | 7 (28.0)                    |         |
| Hispanic             | 1 (4.2)                     | 3 (12.5)                    | 0                           |         |
| **Tobacco consumption, n (%)** |                     |                             |                             | 0.993   |
| Nonsmoker            | 14 (58.3)                   | 13 (54.2)                   | 13 (52.0)                   |         |
| Ex-smoker            | 8 (33.3)                    | 9 (37.5)                    | 10 (40.0)                   |         |
| Smoker               | 2 (8.3)                     | 2 (8.3)                     | 2 (8.0)                     |         |
| **Alcohol history, n (%)** |                         |                             |                             | 0.825   |
| No                   | 15 (62.5)                   | 10 (41.7)                   | 14 (56.0)                   |         |
| Rarely               | 4 (16.7)                    | 5 (20.8)                    | 4 (16.0)                    |         |
| Occasionally         | 3 (12.5)                    | 7 (29.2)                    | 5 (20.0)                    |         |
| Regularly            | 2 (8.3)                     | 2 (8.3)                     | 2 (8.0)                     |         |
| **Weight (kg)**      |                             |                             |                             | 0.216   |
| Mean (SD)            | 86.47 (17.384)              | 95.44 (18.293)              | 88.39 (16.93)               |         |
| Range                | 48.7 to 125.4               | 64.5 to 131.8               | 63.2 to 124.7               |         |
| **Nausea/vomiting history, n (%)** |                        |                             |                             | 0.801   |
| Naive                | 8 (33.3)                    | 6 (25.0)                    | 6 (24.0)                    |         |
| Non-naive            | 16 (66.7)                   | 18 (75.0)                   | 19 (76.0)                   |         |

*For comparing differences between cohorts, P value is based on Kruskal–Wallis rank test for age, weight, and height and based on Fisher’s exact test for sex, ethnicity, tobacco consumption, and alcohol history.

SD, standard deviation.

Figure 2. Percent of patients with complete protection (CP) from emesis by palonosetron treatment cohort. CP (no emesis) rates for 1-, 2-, and 3-day palonosetron regimens over 7 study days (primary end point on right) and for each study day are shown. Error bars mark the 95% confidence intervals for CP. P value (0.43; exact one-sided Jonckheere–Terpstra trend test) indicates no linear trend toward increasing CP rates with increasing doses of palonosetron over the entire 7 study days. *P = 0.015, suggesting a significant trend toward higher CP with increasing doses of palonosetron on day 0.
prevention than the 1-day cohort ($P < 0.01$ and $P < 0.005$, respectively).

The mean number of hours with any nausea for patients receiving 1, 2, or 3 days of palonosetron were 42.4 ± 43.7 (standard deviation), 21.8 ± 34.9, and 20.5 ± 26.4 h, respectively (Figure 4).

During the 2 days of chemotherapy before HSCT, most patients reported little to no interference in daily functioning due to nausea/emesis as reflected in responses to the Osoba questionnaire (Figure 5). During the 5 days post-HSCT, little or no functional impact was reported by the majority of patients receiving two or three doses of palonosetron (70.8% and 56.0%, respectively), as compared with 41.7% of patients in the 1-day palonosetron group.

**safety**
Most AEs were of mild-to-moderate intensity and, in the investigators’ opinion, unrelated to study medication. No patients discontinued treatment due to AEs, no serious AEs occurred that were considered related to study medications, and AEs occurred at similar frequencies in patients treated with 1, 2, or 3 days of palonosetron (Table 2). The most common
This pilot study explored the safety and efficacy of three palonosetron-containing regimens for emesis prevention over 7 days in MM patients receiving 100 mg/m² melphalan and HSCT. Over 40% of patients in each of the palonosetron treatment groups had CP from emesis throughout the entire 7-day study period. These results suggest that palonosetron could be superior to other antiemetic regimens [4–6]. However, considering that 80% of patients either had emesis or required rescue medication even with multiple doses of palonosetron, it is obvious that to achieve the goal of emesis-free patients therapy will need to be explored.

Reducing the burden of therapy of high-dose melphalan for myeloma should become a major focus of study for myeloma transplant researchers. Campagnaro et al. [26] recently reported that protracted nausea was a common occurrence in patients post-autologous stem cell transplant for myeloma and was a significant contributor to symptom burden during the blood cell count nadir phase of transplant. A recent literature review demonstrates that although the combination of a 5HT3 antagonists with or without steroid resulted in good acute control of emesis but delayed CINV remained a significant problem [27]. Thus, reduction of delayed CINV should remain a major target to improve the transplant experience for most patients with myeloma undergoing this treatment [28–31].

Administration schedules of antiemetics also vary widely, some start 1 h before chemotherapy and continue 24 h after [5], while in others, antiemetic therapy extends through the first 2 days of multiple-day treatment regimens [8]. In this study, because of the sample size no definitive conclusions can be made over the benefit of multiple-day administration of palonosetron. No increasing trend in efficacy was noted in the primary end point of overall CP rate with multiple days of palonosetron (P = 0.43). However, on the day of HSCT (day 0), 92% of the patients who received three doses of palonosetron were emesis free compared with 66.7% and 79.2% of those who had received one and two doses of palonosetron, respectively (P = 0.015). Secondary measures of the effects of palonosetron also showed trends that favored multiple days of dosing. Therapy with palonosetron was well tolerated regardless of the number of doses administered. Although the rates of complete remission compare favorably with previous studies of antiemetic prophylaxis in patient populations receiving multiple-day high-dose chemotherapy before HSCT, the majority of patients either had emesis or required rescue medication [4, 5, 22, 28, 32].

Several limitations of this pilot study are worth noting. First, the relatively small sample size limits the precision of the measurements, and no clear recommendations can thus be made based on these results. On day –2, when all three cohorts had received the same therapy (one dose each of i.v. palonosetron and dexamethasone before melphalan), significant trends in some measures of antiemetic efficacy were detected, possibly related to the lack of precision inherent in studies with small sample sizes. Second, corticosteroids were not given on day 0 (day of HSCT) in any cohort. A meta-analysis by Ioannidis et al. [33] confirmed the contribution of dexamethasone to enhancing the antiemetic effects of 5HT3 antagonists chemotherapy.

Aprepitant is a natural killer (NK)-1 receptor antagonist that crosses the blood-brain barrier and exerts it antiemetic effect. There is limited experience with the use of aprepitant in the...
context of stem cell transplantation. Bubalo et al. [32] reported on 40 patients undergoing allocgenic stem cell transplantation who received aprepitant or placebo in conjunction with steroids and a 5HT3 antagonist. Seventeen patients in the aprepitant group had a CR (no emesis and no need for rescue medications as compared with seven in the placebo group, \(P = 0.025\)) [32]. However, Paul et al. [34] found only a 33% CR rate with aprepitant added to a standard steroid plus 5HT3 antagonist regimen. The results of our study would suggest that combining multiple dose palonosetron with aprepitant should be further explored. Although triple therapy (with dexamethasone, a 5HT3 antagonist, and a NK-1 receptor antagonist) is now recommended in the latest antiemetic guidelines for patients receiving highly emetogenic chemotherapy, this needs to be further studied in prospective randomized trials [7, 35].

In conclusion, results from this pilot study encourage further evaluation of multiple-day palonosetron regimens administered in conjunction with dexamethasone for emesis prevention in patients with hematologic malignancies receiving multiple-day high-dose chemotherapy regimens. Additional studies to determine the optimal regimen of palonosetron and dexamethasone with or without other agents are warranted.

funding

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disclosure

All of the authors participated in the conduct of this clinical research study, reviewed and extensively revised the manuscript throughout its development, and gave final approval for submission. This study was sponsored by Helsinn Healthcare, SA, and was funded, designed, conducted, and supervised in full by Eisai, Inc. Eisai staff analyzed study data and oversaw preparation of the clinical study report. All investigators, authors, and coinvestigators were responsible for analysis and interpretation of the data and are the guarantors of the manuscript and its content. SAG, KFM, RTM, JSB, RB, DDH, FLM, and MWS have served as consultants and received research support from MGI/Eisai for this study. EBR and TJD were employed by MGI/Eisai during the conduct of this study. SAG and all co-authors were responsible for writing and editing this manuscript, with additional writing and editorial support provided by Bob Rhoades that was funded by Eisai Inc.

Table 2. Common* AEs considered possibly or probably related to study drug by cohort

<table>
<thead>
<tr>
<th></th>
<th>1-day palonosetron (n = 24), n (%)</th>
<th>2-day palonosetron (n = 24), n (%)</th>
<th>3-day palonosetron (n = 25), n (%)</th>
<th>Total (N = 73), n (%)</th>
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<td>Diarrhea</td>
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<td>6 (24.0)</td>
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<td>4 (16.7)</td>
<td>3 (12.0)</td>
<td>8 (11.0)</td>
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<tr>
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<td>1 (4.2)</td>
<td>3 (12.5)</td>
<td>2 (8.0)</td>
<td>6 (8.2)</td>
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<tr>
<td>Flatulence</td>
<td>0 (0.0)</td>
<td>3 (12.5)</td>
<td>2 (8.0)</td>
<td>4 (5.5)</td>
</tr>
</tbody>
</table>

*Occurring in at least 10% of patients in any cohort.

**None of the AEs were considered by the investigators to be definitely related to study medication.

AEs, adverse events.

references


