Efficacy and safety of palonosetron versus ondansetron in the prevention of chemotherapy-induced nausea and vomiting in paediatric patients with cancer receiving moderately or highly emetogenic chemotherapy: a randomised phase 3 double-blind non-inferiority study

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Summary

Background Palonosetron has demonstrated efficacy in the prevention of chemotherapy-induced nausea and vomiting (CINV) in adult patients undergoing moderately or highly emetogenic chemotherapy. This phase 3 study evaluated the efficacy and safety of palonosetron versus ondansetron in the prevention of CINV in paediatric patients.

Methods In this multicentre, multinational, double-blind study, paediatric patients aged 0–<17 years, naïve or non-naïve to chemotherapy and scheduled to undergo moderately or highly emetogenic chemotherapy for the treatment of malignant disease were randomised centrally 1:1:1 to receive up to four cycles of 10 or 20 μg/kg palonosetron on day 1, or three 150 μg/kg doses of ondansetron on day 1, scheduled 4 hours apart, according to a static central permuted block randomisation scheme by an interactive web response system. Randomisation was stratified according to age and emetogenicity. The primary endpoint was complete response (no vomiting, retching, or use of rescue medication) during the acute phase (0–24 hours post-chemotherapy) of the first on-study chemotherapy cycle, as assessed in the population of randomly assigned patients who received moderately or highly emetogenic chemotherapy and an active study drug. Safety was assessed, according to treatment received, by adverse events, 12-lead electrocardiograms, laboratory and physical assessments, and vital signs. The study, registered with the ClinicalTrials.gov, number NCT01442376, has now been completed.

Findings Between September 12, 2011, and October 26, 2012, 502 patients were randomised to receive 10 μg/kg palonosetron (n=169), 20 μg/kg palonosetron (n=169), or ondansetron (n=164), 493 of whom were included in the efficacy analysis. Most patients (388 [79%] of 493) had previously received chemotherapy and 271 [55%] of 493 received concomitant corticosteroids. Complete responses were recorded in 90 (54·2%) of 166 patients receiving 10 μg/kg palonosetron, 98 (59·4%) of 165 receiving 20 μg/kg palonosetron, and 95 (58·6%) of 162 receiving ondansetron. Non-inferiority (δ=-15%) versus ondansetron was demonstrated for 20 μg/kg palonosetron (weighted sum of difference in complete response rates=0·36%, 97·5% CI -11·7–12·4; p=0·0022). In the first on-study treatment cycle, treatment-emergent adverse events were reported in 134 (80·2%) of 166 patients receiving 10 μg/kg palonosetron, 113 (69·3%) of 165 receiving 20 μg/kg palonosetron, and 134 (81·7%) of 162 receiving ondansetron. The most common drug-related treatment emergent adverse events were nervous system disorders, primarily headache. Drug-related reports of electrocardiogram QT prolonged and sinus tachycardia

were less frequent in patients receiving palonosetron than ondansetron and raised no clinical concerns. The incidence of serious adverse events in the first on-study treatment cycle was lower in the 20 μg/kg palonosetron group (43 [26·4%] of 163 patients) than the 10 μg/kg palonosetron group (52 [31·1%] of 167 patients), and the ondansetron group (55 [33·5%] of 164 patients).

Interpretation Non-inferiority was demonstrated for 20 μg/kg palonosetron during the acute phase of the first on-study chemotherapy cycle. Electrocardiographic investigations and adverse event monitoring raised no concerns, demonstrating that palonosetron is safe in paediatric patients. 20 μg/kg palonosetron is now indicated by the European Medicines Agency for the prevention of CINV in paediatric patients aged 1 month to 17 years.

Funding Helsinn Healthcare.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common and distressing side-effect of moderately and highly emetogenic chemotherapy regimens.[1-3] Adult patients in whom CINV is left uncontrolled experience a severe deterioration in their quality of life and may experience malnourishment, anxiety, and depression. Fear of CINV is sufficient for many patients to postpone or even refuse potentially life-saving treatment.[3-6] However, antiemetics can improve quality of life, increase treatment compliance and effectiveness, and therefore improve patient outcome.[7-9] Antiemetics counter CINV by antagonising the 5-hydroxytryptamine subtype 3 (5-HT_3) receptor or the neurokinin-1 (NK_1) receptor. Currently, in adult patients undergoing highly emetogenic chemotherapy, the administration of a 5-HT_3 receptor antagonist alongside the NK_1 receptor antagonist, aprepitant, and dexamethasone is recommended for the treatment of acute CINV.[10,11] For patients undergoing a moderately emetogenic chemotherapy regimen, palonosetron hydrochloride (Aloxi®, palonosetron; a 5-HT_3 receptor antagonist [Pierre Fabre Medicament Production, Idron, France]) plus dexamethasone is recommended.[11] _ENREF_10

In paediatric patients, at the time of study design, Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO) guidelines recommended prophylactic antiemetic therapy comprising a 5-HT_3 receptor antagonist and dexamethasone to prevent acute CINV in patients scheduled to receive moderately or highly emetogenic chemotherapy.[2] In later guidance, the Pediatric Oncology Group of Ontario (POGO) Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients recommended that children scheduled to receive highly emetogenic therapy should receive antiemetic prophylactic therapy of ondansetron or granisetron plus dexamethasone and aprepitant (≥12 years of age and receiving antineoplastic agents not known to interact with aprepitant) or ondansetron or granisetron plus dexamethasone (<12 years of age or receiving aprepitant interacting agents).[12] For patients scheduled to receive moderately emetogenic chemotherapy, the recommendation in the POGO guidelines is that patients should receive ondansetron or granisetron plus dexamethasone. _ENREF_12

In adult patients receiving moderately emetogenic chemotherapy palonosetron has been shown to be superior as a single agent to ondansetron or dolasetron at preventing both acute and delayed CINV.[13-15] _ENREF_12 Palonosetron has also been shown to have greater

receptor selectivity, longer duration of action, and unique structural characteristics compared with other 5-HT_3 receptor antagonists.[13,16-20] Palonosetron also appears to have an advantageous safety profile compared with ondansetron, granisetron, dolasetron, and tropisetron, which have been associated with electrocardiographic changes and arrhythmias, sometimes leading to the potentially fatal heart rhythm *torsades de pointes*.[13,14,21-24] Palonosetron has been shown not to cause arrhythmias or symptomatic electrocardiographic changes.[25-27]

The present study was designed to assess the efficacy and safety of two intravenous doses of palonosetron (10 and 20 μg/kg) in paediatric patients with cancer aged from new-born (full term; ≥37 weeks) to <17 years, scheduled to undergo moderately or highly emetogenic chemotherapy. The primary objective of this study was to demonstrate in paediatric patients the non-inferiority of palonosetron, versus ondansetron, during the acute phase of the first on-study chemotherapy cycle.

Methods

Study design and participants

This randomised, multinational, phase 3 study was done at 71 sites in the United States, Latin America, Western and Eastern Europe, and Russia. Eligible patients were aged from newborn (full term; ≥37 weeks) to less than 17 years, with a bodyweight of ≥3·2 kg, naïve or non-naïve to chemotherapy, scheduled to receive moderately or highly emetogenic chemotherapy (at the time of study design, a specific paediatric classification system was not available; agents designated in these risk groups for our study are listed in appendix p 1) on study day 1 (of a single-day regimen, or day 1 of a multiple-day regimen), for histologically, cytologically or in the case of brain tumours imaging-confirmed malignant disease. Eastern Cooperative Oncology Group performance status ≤2 was required in patients aged ≥10 years. For patients with known hepatic impairment (defined as aspartate aminotransferase >2·5 x upper limit of normal [ULN] or alanine aminotransferase >2·5 x ULN or total bilirubin >1·5 x ULN), known renal impairment (defined as creatinine >1·5 x ULN) or known history of or predisposition to cardiac abnormalities, inclusion was permitted if in the site investigator's opinion, the existence of any such condition should not have jeopardized patient safety during the study. The use of any corticosteroid included in a chemotherapeutic regimen or to reduce intracranial pressure was permitted. The main exclusion criteria were: patients suffering from ongoing vomiting from any organic aetiology (including patients with

history of gastric outlet obstruction or intestinal obstruction due to adhesions or volvulus); patients with a history of gastric outlet or intestinal obstruction; patients who suffered vomiting, retching or nausea within the 24 hours prior to study drug administration; patients who had received any drug with a potential antiemetic effect within the 24 hours prior to treatment initiation (prior use of domperidone or metoclopramide was excluded; for details of all prohibited drugs, see appendix p 2); patients who had received total body irradiation or radiotherapy of the upper abdomen, cranium, craniospinal regions, or pelvis within one week of study entry; patients with baseline prolongation of the QTc interval >460 ms (this threshold was set following a request from the UK Medicines & Healthcare products Regulatory Agency that we define an acceptable maximal QTc length in relation to patient eligibility).

The study was conducted in accordance with the Declaration of Helsinki (2008) and the International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) E6 guideline. Approval was obtained from the appropriate International Ethics Committees, Institutional Review Boards, and Regulatory Authorities, prior to study initiation. Written informed consent was obtained from parent(s)/legal guardian(s) prior to enrolment. For patients of appropriate age and maturity, signed assent forms were obtained in compliance with local laws and regulations.

Randomisation and masking

Eligible patients were randomised via an interactive web response system (IWRS) that assigned patients to treatment groups using a computer-generated randomisation schedule, stratified (as requested by the United States Food and Drug Administration [FDA]) by emetogenicity of chemotherapy (moderately/highly emetogenic) and age group (<2 years; 2 years up to <6 years; 6 years up to <12 years; 12 years up to <17 years) through static central permuted blocks.

The study was conducted in a double-blind, double-dummy manner. The IWRS provider and a designated Helsinn Healthcare SA employee retained master copies of the randomisation codes in a secure fashion to ensure blinding. Project team members involved in data collection and analysis, and members of the investigator's team, had no access to the randomisation codes. Packaging and labelling of the study drugs were carried out in accordance with all applicable regulatory and legal requirements. All kits were identical in appearance with the exception of the kit number. The double-dummy design was accomplished by using the placebo formulation for palonosetron (identical to the active

formulation but without palonosetron and EDTA), and isotonic saline solution as the placebo for ondansetron.

Procedures

Patients were randomised to one of the following treatment groups: 10 μg/kg palonosetron, up to a maximum dose of 0·75 mg, administered 30 ± 5 minutes before chemotherapy as a 15-minute intravenous infusion; 20 μg/kg palonosetron, up to a maximum dose of 1·50 mg, administered identically to the 10 μg/kg dose or 3 × 150 μg/kg ondansetron, up to a maximum total dose of 32 mg (maximum single dose 10.67 mg: current guidance is that a single intravenous dose must not exceed 8 mg), administered as a 15-minute intravenous infusion 30 ± 5 minutes before chemotherapy, as well as 4 and 8 hours ± 30 minutes after first administration (label-specified administration schedule).

A single palonosetron dose per chemotherapy cycle (day 1) was given to each patient in the two palonosetron groups, regardless of whether the chemotherapy regimen was single day or multiple day. Three ondansetron doses were given to each patient in the ondansetron group on day 1. If a patient was scheduled to receive multiple day chemotherapy, then they could receive any permitted prophylactic medication according to the standard practice of the investigative site on any other treatment days in the chemotherapy cycle beyond day 1. Patients on such schedules, regardless of study treatment group, could therefore potentially receive ondansetron on treatment days subsequent to day 1. Patients could receive study treatment for up to four chemotherapy cycles.

The ondansetron indication is limited to the management of CINV in children aged ≥6 months. However, due to the unmet medical need for antiemetics in younger patients, and at the request of the FDA, we accepted the inclusion of younger patients in our study. With a small number of exceptions (appendix p 3), this off-label use of ondansetron was accepted by all relevant regulatory and ethics committees and site investigators.

Study drug solutions were provided in a standard volume of 0.6 mL/kg total body weight and transferred into a unique final container. Depending on the final volume as determined by the patient's weight, the final container could be a syringe, a vial, or an infusion bag. The first administration, a 15-minute intravenous infusion performed 30 ± 5 minutes before chemotherapy, was prepared as described in the appendix (p 4). For the second and third administrations of ondansetron (4 and 8 hours ± 30 minutes after the first administration), 0·075 mL/kg from the ondansetron/placebo ampoule(s) was diluted in isotonic saline solution (0·525 mL/kg) to a total volume of 0·6 mL/kg and transferred into the final container. Patients

also received concomitant dexamethasone, if deemed appropriate by the site investigator unless this was contraindicated or unless corticosteroids were already included in the chemotherapy cycle; dosing and administration of corticosteroids were according to standard clinical practice. Rescue medication was administered to alleviate established, refractory or persistent nausea or vomiting and was permitted on an as-needed basis (metoclopramide was not permitted; all other medications were permitted as per the standard of care of the site), at the discretion of the site investigator.

Patients were free to withdraw from the study at any time and were not required to provide an explanation for their decision to withdraw. Patients could be removed from the study without their consent for protocol specified reasons, which included safety concerns or non-compliance.

Outcomes

The primary efficacy endpoint was complete response (defined as no vomiting, retching, or use of antiemetic rescue medication) during the acute phase (defined as 0–24 hours after the start of chemotherapy on day 1) of the first on-study chemotherapy cycle. Secondary efficacy endpoints assessed during the first on-study chemotherapy cycle were the proportion of patients who achieved a complete response during the delayed (defined as >24–120 hours after the start of chemotherapy on day 1) and overall phases (defined as 0–120 hours after the start of chemotherapy on day 1). Other secondary efficacy endpoints assessed for each phase (acute, delayed, and overall) were: the proportion of patients without vomiting; the proportion without emetic episodes (defined as one or more continuous vomits [expulsion of stomach contents through the mouth] or retches [an attempt to vomit that is not productive of stomach contents]); the proportion without antiemetic rescue medication; the proportion without nausea (analysis restricted to patients aged ≥6 years); time to first vomiting; time to first emetic episode; time to first administration of rescue medication; and time to treatment failure (time to first emetic episode or first administration of antiemetic rescue medication, whichever occurred first).

In the first on-study treatment cycle, for the assessment of emetic episodes, a diary was provided to the patient or their caregivers; one part of the diary was for the acute phase, the other for the delayed phase. In the diary, each episode of retching and vomiting, as well as any rescue medication administered, was to be entered. Nausea was assessed by a yes/no question in the electronic case report form (eCRF). This question was asked to patients of 6 years of age or older, at the end of the acute and delayed phases (appendix p 3). In subsequent chemotherapy cycles, for the acute and delayed phases, both nausea and

vomiting were assessed by yes/no questions in the electronic case report form (eCRF). Missing data for any single question relating to vomiting and retching, nausea or timing of antiemetic rescue medication intake led to an assessment of failure in relation to complete response.

Primary and secondary efficacy analyses also included summary statistics by age and chemotherapy-related emetogenicity strata.

Safety was assessed on adverse events, physical examinations (performed at screening; days -14 to -1, or -7 to -1 if the patient was aged <2 years, and between days 7 to 10), vital signs (pulse, systolic and diastolic blood pressures; recorded at screening, day 1 – at the end of the first study drug administration, and 1 and 3 hours after the end of the first study drug administration –, and between days 7 to 10), laboratory assessments (haematology, blood chemistry, and urinalysis; blood samples taken at screening and between days 7 to 10 for haematology and chemistry assessments; samples for serum chemistry assessments were taken on day 1, at the end of the first study drug administration), and 12-lead electrocardiograms (recorded in triplicate at screening and between days 7 to 10). In addition, a single electrocardiogram was recorded at the end of the first study drug administration on day 1. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 14·0. All treatment-emergent adverse events, whether non-serious, serious, or adverse drug reactions, had their severity (mild, moderate, or severe), intensity (rated according to the descriptions and grading scales of the Common Terminology Criteria for Adverse Events [CTCAE], version 4·03), and the site investigator's opinion on their relationship to the study drug, recorded. The period for assessing adverse events was specified as up to 18 days after study drug administration on day 1.

Statistical analysis

The full analysis set comprised all randomised patients who received at least one course of moderately or highly emetogenic chemotherapy and an active study drug. The as-treated population was similar to the full analysis set, except that the randomised patients were analysed according to the actual treatment received. The safety population comprised all patients who received at least one dose of study drug and had at least one safety assessment. Safety was analysed according to actual treatment received.

The primary efficacy objective was to demonstrate the non-inferiority of palonosetron, versus ondansetron, during the acute phase (0–24 hours post-chemotherapy) of the first on-study chemotherapy cycle, comparing the difference in the proportions of patients achieving a

complete response with palonosetron (π_T) minus ondansetron (π_R) versus a preset non-inferiority margin (δ=-15%). To be considered as non-inferior to ondansetron, for at least one of the doses of palonosetron, the lower limit of the 97.5% CI for the ΔCR had to be superior to -15%. The elementary null hypothesis (H_0) of no difference between treatments (tested with a type I error of 2·5%) was:

$\pi_T - \pi_R \leq \delta$. Divided into two hypotheses, $H_{0\ 20\ \mu g/kg}$: $\pi_{T\ 20\ \mu g/kg} - \pi_R \leq \delta$ and $H_{0\ 10\ \mu g/kg}$: $\pi_{T\ 10\ \mu g/kg} - \pi_R \leq \delta$

The stratum-adjusted Mantel-Haenszel method was used to calculate 97·5% confidence intervals (CIs) from the weighted sum of the differences in complete response rate (ΔCR). If the lowest bounds of the CIs were strictly superior to the non-inferiority margin, the null hypothesis was rejected. A stratum-adjusted Mantel-Haenszel analysis of the as-treated population and stratum-adjusted Miettinen and Nurminen analyses of the full analysis set and as-treated population,[28] were also performed as co-primary efficacy analyses. The non-inferiority assessment applied only to complete response in acute phase for the first on-study chemotherapy cycle. No adjustment was done for multiple testing in relation to the secondary endpoints. The secondary endpoints were analysed in an exploratory way, by comparing the stratum-adjusted Mantel-Haenszel 95% CIs of the proportional difference to zero; superiority was considered when the 95% CI of the ΔCR did not include 0. Not being included in the powered part of the analysis, these data could not subsequently lead to a label claim.

The sample size for this non-inferiority trial was estimated based upon the following assumptions: a complete response rate in the palonosetron and ondansetron groups of 60% based on previous trial data; type I error of 5% (2-sided); type II error of 20% (power of 80%); non-inferiority margin, set following discussion with the regulatory authority,[29] of -15%. Our study was based on the PALO-99-07 study, in which the palonosetron doses of 3 μg/kg and 10 μg/kg were tested.[30] The dose of 10 μg/kg showed a complete response rate of 54.1% (20/37 patients) during the acute phase. One exclusion criterion in this study was treatment with chemotherapy that required corticosteroids on study day 1. In our study, the use of corticosteroid as part of the chemotherapy was permitted, so the expected complete response rate was slightly increased to 60%. In the case of ondansetron, efficacy results for intravenous administration in a paediatric population, as stated in the FDA label, indicate a complete response rate of 58% and 56%.

To maintain the overall type I error at 5%, the conservative correction of Bonferroni was applied and the 2-sided significance level set to 2·5% for each elementary test. Determination of the sample size had to ensure a disjunctive power of at least 80%. This was achieved using simulations, which showed that from n=155 the lower bound of the 95% CI of the disjunctive power was at least 80% and the estimated power superior to 81·5%. Accordingly, the total sample size was increased to 492 evaluable patients, equally distributed between the three treatment groups (164 patients per group).

SAS® version 9.2 was used for data analyses. The study is registered with ClinicalTrials.gov, number NCT01442376.

Role of the funding source

The funder of the study was responsible for data management and statistical analysis, and designed the study in conjunction with the corresponding author in response to an FDA written request. The funder interpreted the data in collaboration with the authors and commissioned drafting of the manuscript. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Patients

Between September 12, 2011, and October 26, 2012, 502 patients were randomly assigned to treatment. Eight patients did not receive an active study drug and a further patient received chemotherapy of low emetogenic potential; 493 patients were therefore included in the full analysis set and as-treated population (for sites enrolling these patients see appendix p 5, 6), and 494 in the safety population (figure 1). Baseline characteristics for the full analysis set, as summarised in table 1, were generally comparable between the treatment groups. In particular, the distribution of primary cancers was essentially balanced. The majority of patients received moderately emetogenic chemotherapy, most patients had previously received chemotherapy and 271 [55%] of 493 received concomitant corticosteroids. Approximately one half of patients (293 [52%] of 493) received on-study moderately/highly emetogenic chemotherapy as a single day (day 1) regimen, with about three quarter of patients (361 [73%] of 493) treated across multiple days with chemotherapy agents, regardless of the emetogenicity (for further detail of administration schedules, see appendix p 7). The most frequently administered chemotherapeutic agents in the present

study were vinca alkaloids and analogues, and nitrogen mustard analogues (appendix p 8). Corticosteroids use during the first on-study chemotherapy cycle was essentially balanced between treatment groups and is summarised in the appendix (p 9). Dexamethasone was administered for various reason in 32% (106 of 493) of the patients from day 1 to day 6, and in 15% (73 of 493) from day 2 to day 6; other corticosteroids were given less frequently. The mean dose of dexamethasone administered was 7 mg/m²/day.

Efficacy

During the acute phase, complete responses were recorded in 90 (54·2%) of 166 patients receiving 10 μg/kg palonosetron, 98 (59·4%) of 165 patients receiving 20 μg/kg palonosetron, and 95 (58·6%) of 162 patients receiving ondansetron (table 2). The complete response rate was therefore lower in the 10 μg/kg palonosetron group than in the ondansetron group (ΔCR -4·41%; 97·5% CI -16·4–7·6; p=0·024). For the 20 μg/kg palonosetron and ondansetron groups the ΔCR was 0·36%, with non-inferiority demonstrated for this dose of palonosetron as the lower bound of the 97·5% CI of this difference (-11·7–12·4; p=0·0022) was greater than the preset non-inferiority margin (δ=-15%). These findings were validated by co-primary analyses performed on the full analysis set and as-treated population, as detailed in the appendix (p 10).

During the study, corticosteroids were given at some time to 90 (54·2%) of 166 patients receiving 10 μg/kg palonosetron. Of these 90 patients, 42 (46·7%) achieved a complete response, compared with 48 (63·2%) of 76 patients who were not given corticosteroids. Corticosteroids were given to 92 (55·7%) of 165 patients receiving 20 μg/kg palonosetron. Of these 92 patients, 57 (62·0%) achieved a complete response, compared with 41 (56·2%) of 73 patients who were not given corticosteroids. Corticosteroids were given to 89 (54·9%) of 162 patients receiving ondansetron. Of these 89 patients, 55 (61·8%) achieved a complete response, compared with 40 (54·8%) of 73 patients who were not given corticosteroids (appendix p 11). Analysis of complete response rates per age group and chemotherapy-related emetogenicity are presented in the appendix (p 12, 13). No clear trends could be identified in efficacy between age groups that might suggest the need for dose adjustments based on patient age. The same applied to the analysis by emetogenicity.

During the delayed phase, complete responses were recorded in 48 (28·9%) of 166 patients receiving 10 μg/kg palonosetron, 64 (38·8%) of 165 patients receiving 20 μg/kg palonosetron, and 46 (28·4%) of 162 patients receiving ondansetron. The complete response rates were therefore comparable for the 10 μg/kg palonosetron and ondansetron groups (ΔCR 0·42%; 95% CI -9·4–10·3), and higher for the 20 μg/kg palonosetron group

versus the ondansetron group (ΔCR 10·17%; 95% CI -0·1–20·4). It was therefore interesting to note, in an additional analysis performed on the as-treated population, that the 95% CI calculated for the difference between the 20 μg/kg palonosetron and ondansetron groups (ΔCR 11·02%; 95% CI 0·8–21·2) did not include a zero value, indicating that the efficacy of this dose of palonosetron during the delayed phase may be superior to that of ondansetron (appendix p 10).

The proportional differences in complete response rate recorded during the overall phase were similar to those recorded during the delayed phase, with the 20 μg/kg dose of palonosetron being more effective at achieving a complete response than ondansetron (table 2).

In order to further explore the efficacy of study treatments and avoid possibly confounding effects of multiple day chemotherapy in the delayed phase analysis, an exploratory investigation of outcome in the first on-study chemotherapy cycle was carried out in the subset of 254 [52%] of 493 patients who received highly or moderately emetogenic chemotherapy only on day 1 of the on-study chemotherapy regimen (appendix p 14). In each of the acute, delayed and overall phases, higher complete response rates were seen in the 20 μg/kg palonosetron group compared with the 10 μg/kg palonosetron and ondansetron groups.

The proportion of patients who experienced no vomiting in the full analysis set was higher in both palonosetron groups during all phases compared with the ondansetron group (table 3). In particular, the proportions in the 20 μg/kg palonosetron group were higher during the acute (Δ10·03%; 95% CI 1·2–18·8), delayed (Δ15·84%; 95% CI 5·7–26·0), and overall phases (Δ17·46%; 95% CI 7·0–27·9) (table 3).

From the proportions of patients reporting no emetic episodes, greater efficacy was demonstrated for the 20 μg/kg dose of palonosetron than for ondansetron during the acute (Δ11·25%; 95% CI 2·0–20·5), delayed (Δ15·38%; 95% CI 5·1–25·7), and overall (Δ17·56%; 95% CI 7·0–28·1) phases (table 3). For both no vomiting and no emetic episodes endpoints the 95% CIs of the Δ did not include a zero value, indicating that the efficacy of this dose of palonosetron may be superior to that of ondansetron.

The number of patients receiving rescue medication and the type of medication administered was similar across the treatments groups. The proportion of patients who avoided antiemetic rescue medication was lower in the 10 μg/kg palonosetron group during the acute phase,

and comparable during the delayed and overall phases, versus the ondansetron group. The proportion of patients in the 20 µg/kg palonosetron group who avoided antiemetic rescue medication was comparable during the acute phase (Δ-1·23%; 95% CI -10·8–8·3), but higher during the delayed (Δ9·97%; 95% CI -0·6–20·6) and overall phases (Δ8·04%; 95% CI -2·5–18·5), versus the ondansetron group (table 3).

The proportion of patients that did not experience nausea was lower in the 10 µg/kg palonosetron group during the acute phase and higher during the delayed and overall phases, compared with the ondansetron group (table 3). The proportion of patients with no nausea in the 20 µg/kg palonosetron group was marginally higher during the acute phase (Δ4·97%; 95% CI -7·7–17·7) and higher during the delayed (Δ14·79%; 95% CI 1·5–28·1) and overall (Δ15·00%; 95% CI 1·4–28·6) phases compared with the ondansetron group. For the nausea endpoint, the 95% CI of the Δ did not include a zero value, indicating that the efficacy of this dose of palonosetron during the delayed and overall phases may be superior to that of ondansetron.

Safety

The incidence of treatment-emergent adverse events in the first on-study treatment cycle was lower in the 20 µg/kg palonosetron group (113 [69·3%] of 163 patients), than in the 10 µg/kg palonosetron group (134 [80·2%] of 167 patients), and the ondansetron group (134 [81·7%] of 164 patients) (table 4); for seven patients in each treatment group, these were deemed to be drug-related by the investigator, the most common being headache, which accounted for three (1·8%) of 167 patients receiving 10 µg/kg palonosetron, one (<1%) of 163 patients receiving 20 µg/kg palonosetron, and two (1·2%) of 164 patients receiving ondansetron (table 5). Only one drug-related event in one (<1%) of 163 patients in the 20 µg/kg palonosetron group in this first on-study cycle was grade 3 or above (grade 4 infusion site pain). No patients discontinued due to drug-related adverse events. Regarding cardiac disorders, sinus tachycardia accounted for one (<1%) of 167 patients receiving 10 µg/kg palonosetron and two (1·2%) of 164 patients receiving ondansetron, while conduction disorder accounted for one (<1%) of 167 patients receiving 10 µg/kg palonosetron and one (<1%) of 164 patients receiving ondansetron. Electrocardiogram QT prolonged accounted for one (<1%) of 163 patients in the 20 µg/kg palonosetron group and two (1·2%) of 164 patients receiving ondansetron (table 5). The treatment-emergent adverse events recorded in the first on-study chemotherapy cycle and occurring in ≥2% of patients are presented in the appendix (p 15). Treatment emergent adverse events of grade 1–2 in 10% or more of patients in any treatment group, or at grades 3–5 in one or more patients in any treatment group across all on-study treatment cycles are reported in the appendix (p16–20).

The incidence of serious adverse events in the first on-study treatment cycle was lower in the 20 μg/kg palonosetron group (43 [26·4%] of 163 patients) than the 10 μg/kg palonosetron group (52 [31·1%] of 167 patients), and the ondansetron group (55 [33·5%] of 164 patients) (table 4). All were considered to be unrelated to the study drug. Three patients developed adverse events during the first on-study chemotherapy cycle that led to fatal outcomes; one patient receiving ondansetron and highly emetogenic chemotherapy experienced multi-organ failure, pulmonary haemorrhage and staphylococcal sepsis and died on day 15 after initial dosing, one patient receiving ondansetron and moderately emetogenic chemotherapy developed febrile neutropenia and candidiasis and died of a multi-organ failure on 25 day after initial dosing and a third patient receiving 20 μg/kg palonosetron and undergoing moderately emetogenic chemotherapy developed both brain oedema and haemorrhagic stroke on day 1 and died 40 days after initial dosing of multi-organ failure. Four additional patients developed adverse events leading to fatal outcomes after the first on-study chemotherapy cycle. Two deaths occurred in patients in the 20 μg/kg palonosetron group (one due to cardiac arrest and one due to neoplastic progression), and two deaths occurred in patients in the ondansetron group, both due to respiratory failure (one 28 days after receiving the second cycle of ondansetron and one 89 days after initial dosing). No deaths were considered to be related to study drug.

Discussion

Overall, the results of the present study demonstrated that palonosetron, administered at a dose of 20 μg/kg, was non-inferior to ondansetron (a commonly administered therapy) in the prevention of CINV in paediatric cancer patients, aged between 2·1 months (we were unable to enrol neonates) and 16·9 years, during the acute phase of moderately or highly emetogenic chemotherapy regimens. Furthermore, as supported by an exploratory analysis of the subgroup of patients who received a single day (day 1) on-study chemotherapy regimen, the study data suggest that palonosetron, may be more effective than ondansetron during the delayed phase in relation to preventing both vomiting and nausea (conclusions of nausea analysis relate to patients aged 6 years or over). This finding is particularly significant given that the prevention and optimal delay of CINV remains a clinically unmet need, a problem exacerbated by its occurrence generally after hospital discharge, while the patient is not under direct observation.[5] Palonosetron could therefore potentially provide

much needed relief to paediatric cancer patients for up to five days after they have undergone chemotherapy, and following discharge from hospital.

The proportion of patients achieving a complete response was similar for those who did and did not receive concomitant corticosteroids in the 20 µg/kg palonosetron and ondansetron groups, although marginally higher in each case in those who received corticosteroids. Conversely, the number of patients achieving a complete response in the 10 µg/kg palonosetron group was higher for those who did not receive corticosteroids (63·2% versus 46·7% with corticosteroids). It is unclear whether this difference is clinically meaningful or simply due to random variation.

With respect to safety, the types of treatment-emergent adverse events recorded were similar across the three treatment groups. However, a lower incidence of such events was recorded in the 20 µg/kg palonosetron group compared with the ondansetron group and the 10 µg/kg palonosetron group. The treatment-emergent adverse events most frequently reported were consistent with those most commonly observed in cancer patients undergoing chemotherapy; (MedDRA system organ class) blood and lymphatic system disorders, gastrointestinal disorders, and general disorders and administrative site conditions (appendix p 15). The incidence of serious adverse events was also similar across the three treatment groups, with those most frequently recorded, blood and lymphatic system disorders and infections and infestations, also being consistent with those most commonly observed in cancer patients undergoing chemotherapy. The lower incidence of both, treatment-emergent and serious adverse events in the 20 µg/kg palonosetron group compared with the ondansetron group raises the possibility that the safety profile of this particular dose of palonosetron may be better than that of ondansetron.

The majority of treatment-emergent adverse events recorded in each treatment group were deemed by the investigators not to be study drug-related. The most frequently recorded study drug-related treatment-emergent adverse events were (MedDRA system organ class) nervous system disorders, mainly (MedDRA preferred term) headache. With respect to electrocardiogram abnormalities, it is important to note that in contrast to historical studies in adult cancer patients, the incidence of prolonged QT interval was low in the ondansetron group in this study (two [1%] of 164 patients).[13,14] Similarly, the incidence in the palonosetron groups was low, with this event reported for only one (<1%) of 163 patients in the 20 µg/kg group. Throughout the entire study, no study drug related treatment-emergent adverse events with a fatal outcome were recorded, and no patients discontinued the study due to drug-related treatment-emergent adverse events.

To date, few studies have been conducted into the prevention of CINV in paediatric patients, and most involve the 5-HT_3 receptor antagonists granisetron and ondansetron.[31-33] However, palonosetron has been evaluated in one comparative study versus ondansetron and was shown to be safe, efficacious and cost-effective.[34] Other non-controlled studies reported that palonosetron, dosed according to patient's weight at 3 μg/kg and 10 μg/kg, was effective and well tolerated in the paediatric population,[30] and that a single dose of 5 μg/kg of palonosetron without concomitant corticosteroid treatment was effective in preventing both acute and delayed phase CINV in the majority of children with acute lymphoblastic leukaemia treated with high-dose methotrexate.[35]

The inclusion of patients scheduled to receive multiple day (day 1 and additional day[s]) chemotherapy was necessary to enrol enough patients in this large study, given that many paediatric chemotherapy regimens are multiple day; this could potentially have impacted on the evaluation of efficacy. The possibility that the site investigator could make decisions according to local practice, in relation to the use of and dose of dexamethasone/corticosteroids administered, was also a study limitation. However, the chosen model of randomisation and double blind permits these limitations to be overcome when comparing the study treatment groups. In addition we chose not to stratify by use of dexamethasone and schedule of chemotherapy (single day vs multiple day), so as not to increase the number of factors, which might have led to incomplete strata and subsequent problems in the efficacy analysis.

In line with the promising earlier studies, of palonosetron in the paediatric setting, the results of our study showed palonosetron administered at a single dose of 20 μg/kg to be non-inferior to multiple daily doses of ondansetron 150 μg/kg in paediatric patients receiving moderately or highly emetogenic chemotherapy. In addition, we found that palonosetron at a standard dose of 20 μg/kg does not need to be dose adjusted depending on the patient's age. These results led to the approval of the 20 μg/kg dose of palonosetron by both the United States FDA and the European Medicines Agency for the prevention of CINV in paediatric cancer patients aged one month to <17 years undergoing initial or repeated courses of moderately or highly emetogenic chemotherapy. This approval was also to our knowledge the first for an agent capable of preventing acute CINV in patients aged between one and six months (ondansetron is indicated for the management of CINV in children aged between ≥6 months and 18 years). As a substantial fraction of cancers in children are diagnosed during the first year of life,[36] this approval provides a vital new option for children, and especially infants undergoing emetogenic chemotherapy regimens. Also, it has recently

been suggested that the addition of the oral NK_1 receptor antagonist aprepitant to ondansetron with or without dexamethasone may be effective in the prevention of CINV in paediatric patients aged 6 months to 17 years receiving moderately or highly emetogenic chemotherapy regimens.[37] A similar study of palonosetron with aprepitant would be of interest.

Contributors

GK was involved in study co-ordination and governance, the provision of patients, data collection and interpretation and manuscript writing. AW provided patients. EB provided patients and analysed and interpreted the data. TS was responsible for the study concept and design, study co-ordination and governance, data collection and interpretation and manuscript writing. PN was responsible for the study concept and design, study co-ordination and governance, data collection, data analysis and interpretation, manuscript writing and the provision of tables and figures. EK provided patients and was involved in data collection. All authors reviewed the manuscript. A medical writer, Anne Kinsella, drafted the manuscript under the guidance of the authors and subsequently expanded this to a final version according to a series of further discussions with the authors. The final version of the article has been approved by all authors and by the study sponsor.

Declaration of interests

GK reports personal fees, outside the submitted work from Helsinn Healthcare SA; EK reports personal fees from Helsinn Healthcare SA, non-financial support from Helsinn Healthcare SA, and personal fees from Roche, outside the submitted work. AW, EB, TS and PN declare no competing interests.

Acknowledgements

The study was funded by Helsinn Healthcare, SA. The authors would like to thank Dr Gianluca Ballinari of Helsinn Healthcare, SA (Lugano, Switzerland) for collaboration in the writing of the manuscript. Medical writing assistance was provided by Dr Anne Kinsella of Cancer Communications and Consultancy Ltd (Knutsford, UK).

Panel: Research in context

Evidence before this study

The potential efficacy and good safety profile of the 5-HT_3 receptor antagonist, palonosetron, in the management of chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic chemotherapy, as demonstrated in publications comparing palonosetron with ondansetron, dolasetron and granisetron in adult patients, led to studies of the efficacy of palonosetron in paediatric patients with cancer undergoing moderately or highly emetogenic chemotherapy. A search of PubMed (with no time restrictions), abstracts of major oncology and supportive care conferences and ClinicalTrials.gov revealed only one full publication and one abstract reporting on the efficacy of palonosetron in preventing CINV in children undergoing chemotherapy. Indeed the authors of Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update (2011) noted that there was limited research evidence on nausea and vomiting control in special populations, particularly paediatric patients.

This, together with the encouraging results from the study of 100 paediatric patients with cancer undergoing chemotherapy, in which patients were treated either with palonosetron (n=50) or ondansetron (n=50) and monitored for emesis and nausea, led to the decision to undertake a multicentre, randomised, double-blind phase 3 study of palonosetron in a large paediatric population. Ondansetron was chosen as the active comparator because it is one of the most frequently prescribed antiemetic agents and is approved in many countries for intravenous and oral use in adults and children for the prevention of CINV. Additional antiemetics with a CINV indication by the EMA are ondansetron in CINV paediatric patients ≥6 months old and adolescents and granisetron approved in paediatric patients between ≥2 years and 18 years old developing CINV.

Added value of this study

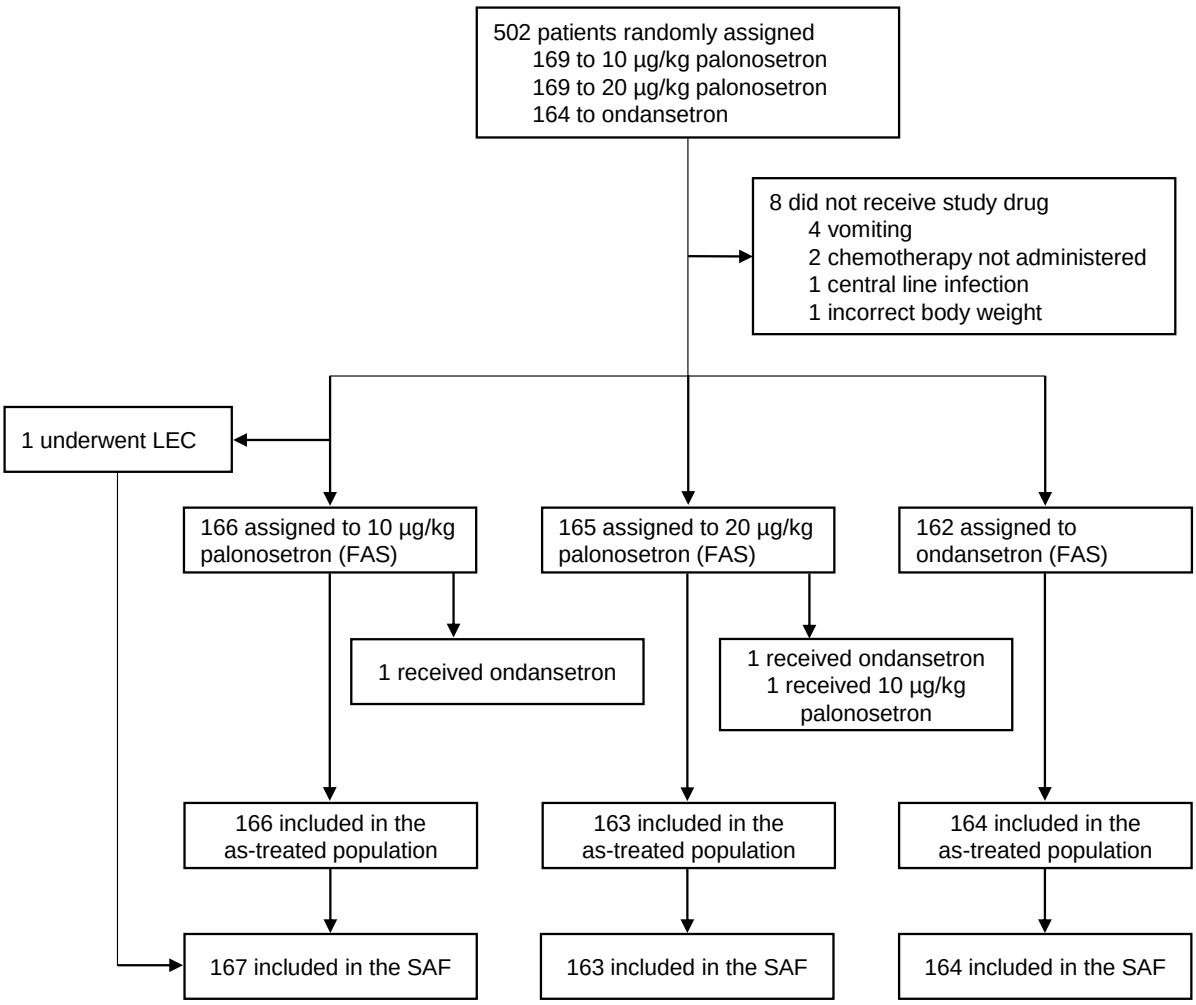
CINV continues to be a distressing side-effect of moderately and highly emetogenic chemotherapy. Antiemetics currently in use include 5-HT_3 receptor antagonists, NK_1 receptor antagonists, and corticosteroids. Such agents are generally used in combination. Palonosetron, has an up to 100-times higher affinity for the 5-HT_3 receptor and a significantly longer half-life, compared with antagonists such as ondansetron, and is therefore potentially more clinically effective. As a single agent in adult patients, palonosetron is more effective than ondansetron and dolasetron at preventing acute and delayed CINV due to moderately emetogenic chemotherapy, and when used in combination with dexamethasone, provides superior control versus ondansetron and granisetron at preventing delayed CINV due to highly emetogenic chemotherapy. Palonosetron is approved in several countries for the prevention of CINV in adult patients following initial and repeated courses of moderately and highly emetogenic chemotherapy. Its safety and efficacy in children has also been

demonstrated in preliminary studies. The current study is part of a paediatric development programme requested by the US Food and Drug Administration and investigates two doses of palonosetron for the prevention of CINV due to moderately or highly emetogenic chemotherapy in paediatric patients.

Implications

The results from the present trial (to our knowledge one of the largest examining the supportive care of paediatric oncology patients undergoing chemotherapy) showed that single-dose 20 µg/kg palonosetron was an effective prophylactic treatment for CINV in paediatric patients aged 0–<17 years, being non-inferior to multiple-dose ondansetron (a commonly administered prophylactic treatment) during the acute phase of moderately or highly emetogenic chemotherapy and potentially superior to ondansetron during the delayed and overall phases. At the 10 µg/kg dose, similar efficacy to ondansetron was observed during the delayed and overall phases. The results of this study led to approval of 20 µg/kg palonosetron by the US Food and Drug Administration and the European Medicines Agency for the prevention of CINV in paediatric patients aged from one month to <17 years – to our knowledge, the first approval of an agent capable of preventing acute CINV in patients aged one to six months.

Figure 1. Trial profile



FAS=full analysis set; LEC=chemotherapy of low emetogenicity; SAF=safety population.

Table 1. Patient baseline and disease characteristics (full analysis set)

		Palonosetron 10 µg/kg (n=166)	Palonosetron 20 µg/kg (n=165)	Ondansetron 3 × 150 µg/kg (n=162)
Gender				
Male		88 (53%)	76 (46%)	98 (60%)
Female		78 (47%)	89 (54%)	64 (40%)
Ethnic origin				
White (not Hispanic)		136 (82%)	139 (84%)	150 (93%)
White (Hispanic)		20 (12%)	15 (9%)	9 (6%)
Mixed: white and Native Indian (Hispanic)		5 (3%)	11 (7%)	3 (2%)
Asian (not Hispanic)		2 (1%)	0	0
Black or African-American (not Hispanic)		2 (1%)	0	0
Latino (Hispanic)		1 (<1%)	0	0
Age, years				
Mean (SD)		8·07 (4·81)	8·39 (4·91)	8·18 (5·17)
Median		7·08	7·85	6·62
Range		0·21–16·87	0·24–16·87	0·18–16·92
ECOG PS				
Number that underwent an assessment		60 (36%)	70 (42%)	61 (38%)
Grade 0		18 (30%)	28 (40%)	24 (39%)
Grade 1		36 (60%)	38 (54%)	36 (59%)
Grade 2		6 (10%)	4 (6%)	1 (2%)
Receipt of prior medications*				
Prior antiemetic medications		72 (43%)	77 (47%)	71 (44%)
Prior medications excluding antiemetics		113 (68%)	129 (78%)	127 (78%)
Naïvety to chemotherapy				
Naïve		39 (23%)	35 (21%)	31 (19%)
Non-naïve		127 (77%)	130 (79%)	131 (81%)
Stratification by emetogenicity and age				
MEC	<2 years	8 (5%)	8 (5%)	9 (6%)
	2–<6 years	35 (21%)	40 (24%)	36 (22%)
	6–<12 years	32 (19%)	33 (20%)	33 (20%)
	12–<17 years	37 (22%)	35 (21%)	33 (20%)
HEC	<2 years	7 (4%)	7 (4%)	6 (4%)
	2–<6 years	19 (11%)	14 (8%)	18 (11%)
	6–<12 years	14 (8%)	13 (8%)	11 (7%)
	12–<17 years	14 (8%)	15 (9%)	16 (10%)
On-study chemotherapy schedule (MEC/HEC agents only)				
Day 1 only		79 (48%)	83 (50%)	92 (57%)
Day 1 and another day(s) (2–6)‡		87 (52%)	82 (50%)	70 (43%)
Tumour extent at study entry				
Primary disease		112 (67%)	118 (72%)	113 (70%)
Metastatic disease		47 (28%)	38 (23%)	41 (25%)
Local recurrence		7 (4%)	9 (5%)	8 (5%)
Most common primary cancers†				
Acute lymphocytic leukaemia		18 (11%)	21 (13%)	23 (14%)
Nephroblastoma		17 (10%)	15 (9%)	7 (4%)
Rhabdomyosarcoma		17 (10%)	8 (5%)	13 (8%)
Neuroblastoma		13 (8%)	10 (6%)	11 (7%)
Medulloblastoma		14 (8%)	10 (6%)	9 (6%)
B precursor type acute leukaemia		11 (7%)	8 (5%)	12 (7%)
Ewing's sarcoma		5 (3%)	11 (7%)	9 (6%)
Hodgkin's disease		8 (5%)	10 (6%)	6 (4%)
Bone sarcoma		8 (5%)	11 (7%)	3 (2%)
Non-Hodgkin's lymphoma		2 (1%)	6 (4%)	7 (4%)

Hodgkin's disease nodular sclerosis stage unspecified	1 (<1%)	8 (5%)	2 (1%)
Primitive neuroectodermal tumour	4 (2%)	2 (1%)	5 (3%)
Hodgkin's disease mixed cellularity stage unspecified	4 (2%)	2 (1%)	3 (2%)
Acute myeloid leukaemia	5 (3%)	2 (1%)	0
Ependymoma malignant	0	2 (1%)	5 (3%)
Optic tract glioma	1 (<1%)	5 (3%)	1 (<1%)
T-cell type acute leukaemia	0	2 (1%)	5 (3%)
Other	37 (22%)	29 (18%)	39 (24%)
Missing	1 (<1%)	3 (2%)	2 (1%)

Data are n (%) unless otherwise stated. *Taken within 14 days prior to day 1 of the first on-study chemotherapy cycle. †Reported in ≥2% of patients in any treatment group. ‡The number of patients receiving moderately or highly emetogenic chemotherapy on day 1 and at least one other day (2–6) in the first on-study chemotherapy cycle calculated by subtracting the number of patient in the subset receiving chemotherapy only on day 1 from the total number in the full analysis set.

ECOG PS=Eastern Cooperative Oncology Group performance status; HEC=highly emetogenic chemotherapy; MEC=moderately emetogenic chemotherapy; SD=standard deviation.

Table 2. Complete response rates during all phases of the first on-study chemotherapy cycle (full analysis set)

	Palonosetron 10 µg/kg (n=166)	**Palonosetron 20 µg/kg (n=165)**	**Ondansetron 3 × 150 µg/kg (n=162)**
Acute phase			
Patients with CR	90 (54·2%)	98 (59·4%)	95 (58·6%)
ΔCR*	-4·41%	0·36%	
97·5% CI (MH analysis)	-16·4–7·6	-11·7†–12·4	
p-value	0·024	0·0022	
Delayed phase			
Patients with CR	48 (28·9%)	64 (38·8%)	46 (28·4%)
ΔCR*	0·42%	10·17%	
95% CI (MH analysis)	-9·4–10·3	-0·1–20·4	
Overall phase			
Patients with CR	39 (23·5%)	54 (32·7%)	39 (24·1%)
ΔCR*	-0·60%	8·25%	
95% CI (MH analysis)	-10·0–8·8	-1·6–18·1	

*ΔCR=weighted sum of Δcomplete response rate palonosetron group minus weighted sum of Δcomplete response rate ondansetron group. †Greater than the preset non-inferiority margin (-15%). CI=confidence interval; CR=complete response; MH=Mantel-Haenszel.

Table 3. Proportions of patients with no vomiting or emetic episodes, and who avoided antiemetic rescue medication, during all phases of the first on-study chemotherapy cycle (full analysis set)

	Palonosetron 10 µg/kg (n=166)	**Palonosetron 20 µg/kg (n=165)**	**Ondansetron 3 × 150 µg/kg (n=162)**
Acute phase			
Patients with no vomiting	133 (80·1%)	138 (83·6%)	119 (73·5%)
Δ*	6·60%	10·03%	
95% CI	-2·4–15·7	1·2–18·8	
Patients with no emetic episodes	122 (73·5%)	132 (80·0%)	111 (68·5%)
Δ*	5·12%	11·25%	
95% CI	-4·5–14·7	2·0–20·5	
Patients avoiding antiemetic rescue medication	115 (69·3%)	124 (75·2%)	123 (75·9%)
Δ*	-6·83%	-1·23%	
95% CI	-16·4–2·8	-10·8–8·3	
	(n=97)	(n=96)	(n=93)
Patients aged ≥6 years with no nausea	63 (64·9%)	69 (71·9%)	62 (66·7%)
Δ*	-2·02%	4·97%	
95% CI	-14·7–10·7	-7·7–17·7	
Delayed phase			
Patients with no vomiting	113 (68·1%)	122 (73·9%)	94 (58·0%)
Δ*	10·08%	15·84%	
95% CI	-0·1–20·3	5·7–26·0	
Patients with no emetic episodes	102 (61·4%)	113 (68·5%)	86 (53·1%)
Δ*	8·46%	15·38%	
95% CI	-1·9–18·8	5·1–25·7	
Patients avoiding antiemetic rescue medication	64 (38·6%)	75 (45·5%)	57 (35·2%)
Δ*	3·21%	9·97%	
95% CI	-7·3–13·7	-0·6–20·6	
	(n=97)	(n=96)	(n=93)
Patients aged ≥6 years with no nausea	55 (56·7%)	63 (65·6%)	47 (50·5%)
Δ*	5·86%	14·79%	
95% CI	-7·7–19·5	1·5–28·1	
Overall phase			
Patients with no vomiting	98 (59·0%)	114 (69·1%)	83 (51·2%)
Δ*	7·97%	17·46%	
95% CI	-2·6–18·5	7·0–27·9	
Patients with no emetic episodes	87 (52·4%)	105 (63·6%)	74 (45·7%)
Δ*	7·00%	17·56%	
95% CI	-3·6–17·6	7·0–28·1	
Patients avoiding antiemetic rescue medication	60 (36·1%)	69 (41·8%)	54 (33·3%)
Δ*	2·63%	8·04%	
95% CI	-7·8–13·0	-2·5–18·5	
	(n=97)	(n=96)	(n=93)
Patients aged ≥6 years with no nausea	46 (47·4%)	56 (58·3%)	40 (43·0%)
Δ*	4·21%	15·00%	
95% CI	-9·3–17·7	1·4–28·6	

*Δ=weighted sum of percentage incidence palonosetron group minus weighted sum of percentage incidence ondansetron group.
CI=confidence interval.

Table 4. Treatment-emergent adverse events recorded in the first on-study chemotherapy cycle (safety population)

	Palonosetron 10 µg/kg (n=167)	**Palonosetron 20 µg/kg (n=163)**	**Ondansetron 3 × 150 µg/kg (n=164)**
At least one TEAE	134 (80·2%)	113 (69·3%)	134 (81·7%)
At least one drug-related TEAE	7 (4·2%)	7 (4·3%)	7 (4·3%)
At least one SAE	52 (31·1%)	43 (26·4%)	55 (33·5%)
At least one drug-related SAE	0	0	0
At least one severe AE	41 (24·6%)	34 (20·9%)	41 (25·0%)
At least one drug-related severe AE	0	0	0
Fatal TEAE	0	1 (<1%)	2 (1·2%)
Fatal drug-related TEAE	0	0	0
Withdrawals due to TEAE	0	2 (1·2%)	1 (<1)
Withdrawals due to drug-related TEAE	0	0	0

Data are n (%).
AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Table 5. Drug-related treatment-emergent adverse by MedDRA system organ class and preferred term in the first on-study chemotherapy cycle (safety population)

MedDRA SOC MedDRA PT	**Palonosetron 10 µg/kg (n=167)**	**Palonosetron 20 µg/kg (n=163)**	**Ondansetron 3 × 150 µg/kg (n=164)**
At least one drug-related TEAE	**7 (4·2%)**	**7 (4·3%)**	**7 (4·3%)**
Nervous system disorders	3 (1·8%)	3 (1·8%)	2 (1·2%)
Headache	3 (1·8%)	1 (<1%)	2 (1·2%)
Dizziness	1 (<1%)	1 (<1%)	0
Dyskinesia	0	1 (<1%)	0
Cardiac disorders	1 (<1%)	0	2 (1·2%)
Sinus tachycardia	1 (<1%)	0	2 (1·2%)
Conduction disorder	1 (<1%)	0	1 (<1%)
Investigations	0	1 (<1%)	2 (1·2%)
Electrocardiogram QT prolonged	0	1 (<1%)	2 (1·2%)
Skin and subcutaneous tissue disorders	0	2 (1·2%)	1 (<1%)
General disorders and administrative site conditions	1 (<1%)	1 (<1%)	0
Musculoskeletal and connective tissue disorders	0	0	1 (<1%)
Respiratory, thoracic, and mediastinal disorders	2 (1·2%)	0	0

Data are n (%).
PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.

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