Phase 3 efficacy and safety study of palonosetron IV infusion versus IV bolus for chemotherapy-induced nausea and vomiting (CINV) prophylaxis following highly emetogenic chemotherapy (HEC)

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BACKGROUND

- Palonosetron (PALO) is a pharmacologically and clinically distinct second-generation 5-hydroxytryptamine-3 receptor antagonist (5-HT_3RA) approved for prevention of nausea and vomiting associated with HEC and moderately emetogenic chemotherapy (MEC).[1-4]
- PALO is the preferred 5-HT_3RA for CINV prophylaxis in patients receiving MEC in antiemetic guidelines from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN).[5,6]
- In antiemetic guidelines from the Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) PALO is the preferred 5-HT_3RA for anthracycline-cyclophosphamide regimens when a neurokinin-1 (NK_1) RA is not available.[7]
- PALO is approved as an intravenous (IV) formulation, with PALO 0.25 mg administered as a 30-sec IV bolus, and as an oral formulation of a 0.50-mg PALO capsule.[3,4]
- A previous phase 1 pharmacokinetic study showed equivalence, in terms of systemic concentrations, between a 15-min IV infusion of 0.25 mg PALO and the approved 0.25-mg PALO IV 30-sec bolus.[8]
- PALO 0.50 mg is present in the approved oral fixed combination agent NEPA, with the second component, the NK_1RA netupitant. Oral NEPA is used for prevention of acute and delayed CINV in patients receiving MEC and HEC.
- Currently, an IV fixed combination of NEPA is undergoing FDA evaluation. NEPA IV:
  - Combines PALO (0.25 mg) and fosnetupitant, a water-soluble phosphorylated netupitant prodrug (235 mg)
  - Is administered as a 30-min infusion with oral dexamethasone before HEC

METHODS

Objectives

- Primary objective: To demonstrate the noninferiority of a single-dose PALO 0.25-mg IV 30-min infusion versus a single-dose PALO 0.25-mg IV 30-sec bolus, in terms of proportion of patients with complete response (CR) in the acute phase (0–24 hours [h] after the start of chemotherapy) following HEC.
- Secondary objective: To evaluate the safety of a single-dose PALO 0.25-mg IV 30-min infusion in patients receiving HEC.

Study Design

- Phase 3 multinational, randomized, double-blind, parallel-group study in chemotherapy-naive patients with malignant solid tumors (NCT02557035).
- Patients, stratified by gender and country, were randomly assigned (1:1) to receive before the start of the reference HEC regimen on day 1:
  - PALO 0.25 mg (50-mL solution) administered as a 30-min IV infusion; or
  - PALO 0.25 mg (5-mL solution) administered as a 30-sec IV bolus
- Oral dexamethasone was administered on day 1 (20 mg, single dose) and days 2–4 (8 mg twice a day) to patients in both groups.

Eligibility criteria

- Key patient inclusion and exclusion criteria are summarized in **Table 1**.

Table 1: Overview of main patient eligibility criteria

Inclusion
≥18 years of age
Naive to cytotoxic chemotherapy (previous biological or hormonal therapy allowed)
Scheduled to receive the first course of a reference HEC* (alone or in combination with other agents[†,‡]) on day 1: – Cisplatin (single IV dose of ≥70 mg/m²); cyclophosphamide ≥1500 mg/m²; carmustine (BCNU) >250 mg/m²; dacarbazine (DTIC); mechlorethamine (nitrogen mustard)
ECOG performance status 0–2
Exclusion
Scheduled to receive MEC or HEC from days 2 to 5
Received or scheduled to receive radiotherapy to the abdomen or pelvis within 1 week prior to the start of reference HEC or between days 1 to 5
Any vomiting, retching, or nausea (grade ≥1) within 24 hours prior to the start of reference HEC
Systemic corticosteroid within 72 hours prior to the start of reference HEC

5-HT_3RA: 5-hydroxytryptamine-3 receptor antagonist; **ECOG:** Eastern Cooperative Oncology Group; **HEC:** highly emetogenic chemotherapy; **IV:** intravenous; **MEC:** moderately emetogenic chemotherapy.
*Reference HEC: To be completed within 4 h
†Additional HEC or MEC agents: To be completed ≤6 h after the start of reference HEC
‡Additional low or minimally emetogenic chemotherapies: Administered at any time after the start of reference HEC

Assessments

- Efficacy was assessed from the start of the reference HEC on day 1, defined as "time 0" to 120 h after. Efficacy parameters were evaluated in the acute (0–24 h), delayed (>24–120 h), and overall (0–120 h) phases.
- Patients completed 2 diaries covering the acute and delayed phases, respectively.
- Patients reported the date and time of any emetic (retching or vomiting) episode and intake of rescue medication in their diary.
- The primary efficacy endpoint was CR (no emesis, no rescue medication) rate in the acute phase.
  - The stratum-adjusted Cochran-Mantel-Haenszel (CMH) method for difference in proportions, stratified by gender and country, with a 2-sided 99% confidence interval (CI) was used for the noninferiority hypothesis testing
- Secondary efficacy endpoints included: CR rate in the delayed and overall phases, and no emesis and no rescue medication rates in the acute, delayed, and overall phases.
  - Comparison between treatments was performed using the same CMH method for the risk difference as for the primary endpoint and relative 2-sided 95% CI. No test for noninferiority was performed
- Efficacy analyses were performed on the full analysis set (FAS) and for the primary endpoint also on the per-protocol population.
- Safety was evaluated based on the frequency and severity of treatment-emergent adverse events (TEAEs), vital signs, 12-lead electrocardiogram, physical examination, and laboratory parameters. AE severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.[9] Safety analyses were performed on the safety population.

Sample size determination

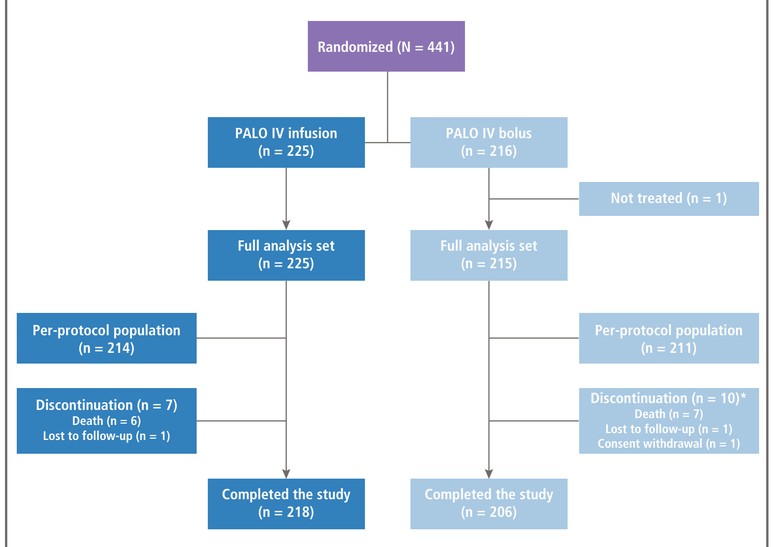
- Sample size was calculated based on the assumption of an 80% CR rate in the acute phase for both groups, with a noninferiority margin of –15%. For a 2-sided test for the difference using type I error equal to 0.01, a total of 212 evaluable patients per group was calculated to be needed to ensure 90% power. The number was increased to 220 per group to ensure an adequate number of evaluable patients.

RESULTS

Patients

- A total of 441 patients were randomized, of which 440 received the study drug and were included in the safety population. Patient disposition is shown in **Figure 1**.
- Main patient demographics and baseline characteristics were similar in both groups (**Table 2**).

Figure 1. CONSORT diagram of patient disposition.



IV: intravenous; **PALO:** palonosetron.
*Includes the patient withdrawn before treatment

Table 2: Patient demographics and baseline characteristics – Full analysis set

Characteristic	PALO 0.25 mg IV 30-min infusion (N = 225)	PALO 0.25 mg IV 30-sec bolus (N = 215)	Total (N = 440)
Gender, n (%)			
Male	151 (67.1)	144 (67.0)	295 (67.0)
Female	74 (32.9)	71 (33.0)	145 (33.0)
Race, n (%)			
White	225 (100)	215 (100)	440 (100)
Age, mean (SD), years	59.9 (8.7)	58.9 (8.5)	59.4 (8.6)
ECOG PS, n (%)			
0	97 (43.1)	109 (50.7)	206 (46.8)
1	120 (53.3)	100 (46.5)	220 (50.0)
2	8 (3.6)	6 (2.8)	14 (3.2)
Primary cancer location, n (%)			
Lung/respiratory tract	119 (52.9)	106 (49.3)	225 (51.1)
Head and neck	32 (14.2)	44 (20.5)	76 (17.3)
Ovarian	13 (5.8)	11 (5.1)	24 (5.5)
Gastric	8 (3.6)	12 (5.6)	20 (4.5)
Bladder	4 (1.8)	4 (1.9)	8 (1.8)
Other*	49 (21.8)	38 (17.7)	87 (19.8)
Extent, n (%)			
Primary	113 (50.2)	116 (54.0)	229 (52.0)
Metastatic	101 (44.9)	90 (41.9)	191 (43.4)
Local recurrence	11 (4.9)	9 (4.2)	20 (4.5)
Reference HEC,† n (%)			
Cisplatin, mg/m²	217 (96.4)	211 (98.1)	428 (97.3)
Dacarbazine, mg/m²	8 (3.6)	4 (1.9)	12 (2.7)
Concomitant chemotherapy days 1–5, n (%)	191 (84.9)	180 (83.7)	371 (84.3)
Etoposide	45 (20.0)	31 (14.4)	76 (17.3)
Gemcitabine	38 (16.9)	31 (14.4)	69 (15.7)
Fluorouracil	21 (9.3)	32 (14.9)	53 (12.0)
Other	87 (38.7)	86 (40.0)	173 (39.3)

*Other main locations: including, but not limited to, reproductive system and skin
†No patient received mechlorethamine, cyclophosphamide, or carmustine
ECOG PS: Eastern Cooperative Group performance status; **HEC:** highly emetogenic chemotherapy; **IV:** intravenous; **PALO:** palonosetron; **SD:** standard deviation

Efficacy

Primary Efficacy Endpoint: CR in the Acute Phase

- In the FAS, a total of 186 (82.7%) patients in the IV 30-min infusion and 186 (86.5%) in the IV 30-sec bolus groups reported CR in the acute phase.
- Noninferiority of PALO 0.25 mg IV 30-min infusion versus 30-sec IV bolus was demonstrated:
  - The risk difference between the 2 groups was –3.8% (99% CI, –12.2%, 4.7%), with the lower limit of the 99% CI for the difference being greater (ie, closer to 0) than the predefined noninferiority margin of –15%. The p value associated to noninferiority testing was <0.001
- Noninferiority of PALO IV 30-min infusion was also shown in the per-protocol population (**Table 3**).

Table 3: Complete response in the acute phase (0–24 h)

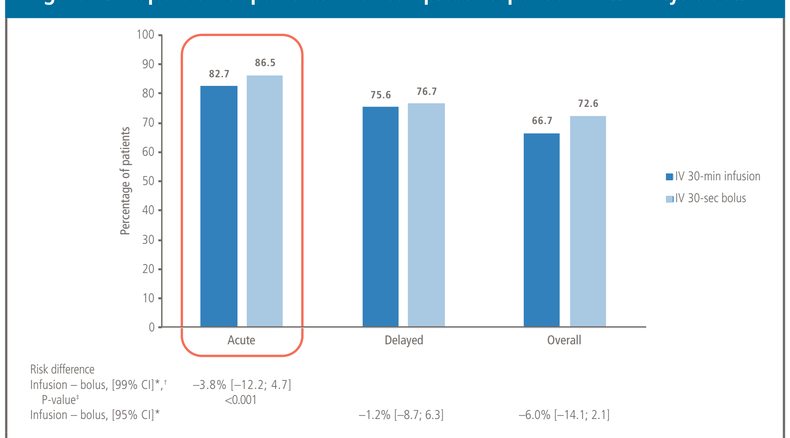
	PALO 0.25 mg IV 30-min infusion	PALO 0.25 mg IV 30-sec bolus
Full analysis set		
N	225	215
CR, n (%) [95% CI]*	186 (82.7) [77.2, 87.1]	186 (86.5) [81.3, 90.4]
CMH risk difference % (infusion – bolus), [99% CI]†	–3.8 [–12.2; 4.7]	
P-value‡	<0.001	
Per-protocol population		
N	214	211
CR, n (%) [95% CI]*	177 (82.7) [77.1, 87.2]	182 (86.3) [81.0, 90.3]
CMH risk difference % (infusion – bolus), [99% CI]†	–3.4 [–12.0; 5.2]	
P-value‡	<0.001	

*Wilson score method CI
†CMH stratum-adjusted method for difference in proportions, stratified by gender and country.[10,11] Predefined noninferiority margin was –15%
‡p value associated with noninferiority testing
CI: confidence interval; **CMH:** Cochran-Mantel-Haenszel; **CR:** complete response; **IV:** intravenous; **PALO:** palonosetron

Secondary Efficacy Endpoints: CR (delayed and overall)/no emesis/no rescue medication

- CR rates in the delayed and overall phases were similar in the PALO IV 30-min infusion and IV 30-sec bolus groups (**Figure 2**).

Figure 2. Proportion of patients with complete response – Full analysis set.

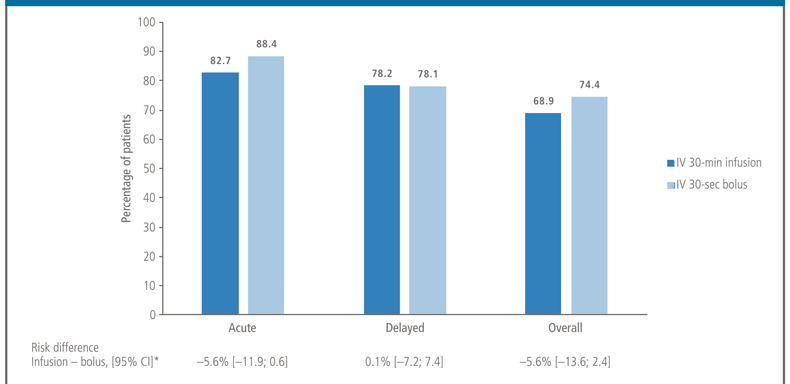


	Acute	Delayed	Overall
Risk difference Infusion – bolus, [99% CI]*,†	–3.8% [–12.2; 4.7]		
P-value‡	<0.001		
Infusion – bolus, [95% CI]*		–1.2% [–8.7; 6.3]	–6.0% [–14.1; 2.1]

*CMH stratum-adjusted method for difference in proportions, stratified by gender and country[10,11]
†Predefined noninferiority margin was –15%
‡p value associated with noninferiority testing
CI: confidence interval; **CMH:** Cochran-Mantel-Haenszel; **CR:** complete response; **IV:** intravenous.

- The proportion of patients with no emetic episodes in the acute, delayed, and overall phases was similar between the PALO IV 30-min infusion and IV 30-sec bolus groups (**Figure 3**).

Figure 3. Proportion of patients with no emesis – Full analysis set.

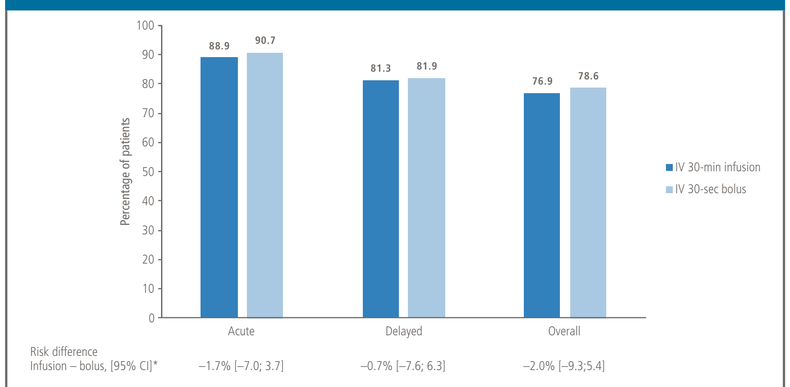


	Acute	Delayed	Overall
Risk difference Infusion – bolus, [95% CI]*	–5.6% [–11.9; 0.6]	0.1% [–7.2; 7.4]	–5.6% [–13.6; 2.4]

*CMH stratum-adjusted method for difference in proportions, stratified by gender and country[10,11]
CI: confidence interval; **CMH:** Cochran-Mantel-Haenszel; **IV:** intravenous.

- The rates of no rescue medication in the acute, delayed, and overall phases were similar between the PALO IV 30-min infusion and IV 30-sec bolus groups (**Figure 4**).

Figure 4. Proportion of patients with no rescue medication – Full analysis set.



	Acute	Delayed	Overall
Risk difference Infusion – bolus, [95% CI]*	–1.7% [–7.0; 3.7]	–0.7% [–7.6; 6.3]	–2.0% [–9.3;5.4]

*CMH stratum-adjusted method for difference in proportions, stratified by gender and country[10,11]
CI: confidence interval; **CMH:** Cochran-Mantel-Haenszel; **IV:** intravenous.

Safety

- The summary of TEAEs in patients receiving 0.25 mg PALO administered as an IV 30-min infusion and IV 30-sec bolus is shown in **Table 5**.

Table 5. Overview of patients with TEAEs – Safety population

	PALO 0.25 mg IV 30-min infusion (N = 225)	PALO 0.25 mg IV 30-sec bolus (N = 215)	Total (N = 440)
Any TEAE, n (%)	85 (37.8)	77 (35.8)	162 (36.8)
Study-drug–related TEAEs	8 (3.6)	3 (1.4)	11 (2.5)
Severe TEAE, n (%)	16 (7.1)	18 (8.4)	34 (7.7)
Study-drug–related severe TEAE	1* (0.4)	0	1 (0.2)
Serious TEAE, n (%)	15 (6.7)	12 (5.6)	27 (6.1)
Study-drug–related serious TEAE	1* (0.4)	0	1 (0.2)
TEAE leading to death, n (%)	6 (2.7)	7 (3.3)	13 (3.0)
Study-drug–related TEAE leading to death	1* (0.4)	0	1 (0.2)
TEAE leading to withdrawal, n (%)	0	0	0

*One patient with grade 4 dyspnea and grade 5 atrial flutter leading to death
IV: intravenous; **n:** number of patients with TEAEs per study arm or total; **N:** number of patients per study arm or total; **PALO:** palonosetron; **TEAE:** treatment-emergent adverse event.

- The frequency and severity of all reported TEAEs were similar for the IV 30-min infusion and IV 30-sec bolus groups.
- Most of the patients experienced TEAEs of mild intensity in both treatment groups.
- One patient in the IV 30-min infusion group experienced 2 study drug-related severe TEAEs: atrial flutter (leading to death) and dyspnea (grade 4). Both events were classified as serious TEAEs.
- There were no interruptions of the infusion among patients in the IV 30-min infusion group. No study drug-related skin/injection site reactions were reported.

CONCLUSIONS

- Noninferiority of PALO 0.25 mg administered as a 30-min IV infusion compared with a 30-sec IV bolus was demonstrated.
- Results of secondary endpoints (ie, proportion of patients with no emetic episodes and of patients with no rescue medication) in the acute phase further support the noninferiority claim.
- The proportions of patients with CR, of patients with no emetic episodes, and of patients with no rescue medication in the delayed and overall phases were also similar between the 2 groups.
- The safety profile of the IV 30-min infusion was comparable to that of IV 30-sec bolus, with most patients experiencing TEAEs of mild intensity.
- In conclusion, a 30-min IV infusion of PALO 0.25 mg appears to be a safe and effective alternative to the approved 30-sec IV bolus administration for the prevention of CINV in patients with malignant solid tumors undergoing HEC regimens.
- These results support the use of PALO as a suitable component of the NEPA IV formulation, currently under FDA review.

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