Safety of Intravenous (IV) NEPA and Oral NEPA for Prevention of CINV in Patients with Breast Cancer Receiving Anthracycline/Cyclophosphamide (AC) Chemotherapy

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BACKGROUND

- As a combination antiemetic of an NK₁RA (netupitant) and 5-HT₃RA (palonosetron), NEPA uniquely offers 5-day CINV prevention with a single dose.
- To offer ease and efficiency for patients and healthcare providers, a fixed IV combination formulation of NEPA was developed using fosnetupitant, a water-soluble phosphorylated pro-drug of netupitant.
- Unlike other NK₁RAs, fosnetupitant does not require any surfactant (e.g., polysorbate 80), emulsifier, or solubility enhancer and contains no allergenic excipients (e.g., egg, soy), thereby minimizing the risk of infusion-related toxicities.
- Following demonstrated pharmacokinetic bioequivalence of IV fosnetupitant and oral netupitant, a Phase 3 registration study leading to the approval of IV NEPA in the United States was conducted to evaluate the safety and tolerability of IV NEPA (relative to oral NEPA) in patients mainly receiving cisplatin-based chemotherapy¹.
- In the study IV NEPA was well tolerated, with a similar safety and efficacy profile as oral NEPA. Importantly, there were no injection-site reactions related to IV NEPA over repeated cycles and no instance of anaphylaxis with either formulation of NEPA. This is noteworthy as hypersensitivity reactions and anaphylaxis have been reported with IV fosaprepitant²⁻⁷, HTX-019 (IV aprepitant)^{8,9}, and IV rolapitant^{12,13}.
- As studies have shown a differential impact of fosaprepitant on infusion-site adverse events (AEs) with patients receiving AC chemotherapy at higher risk⁶⁻¹⁰ compared with those receiving cisplatin-based chemotherapy, it was important to evaluate the safety of IV NEPA in the AC setting.

METHODS

Objectives

- This Phase 3b study was designed to primarily evaluate the overall safety and tolerability of a single dose of IV NEPA over initial and repeated cycles of AC-based chemotherapy.
- A secondary objective was to explore the efficacy of IV NEPA.

Study Design and Treatment Groups

- This was a Phase 3b, multinational, multicenter, randomized, double-blind/double-dummy, parallel-group, multiple cycle study [NCT03403712] conducted in the United States, Russia, Ukraine, and Georgia.
- Eligible patients, stratified by region (US; non-US) and age class (< 55 years; ≥ 55 years) were randomized 1:1 to receive either:
 - a single 30-minute 50 mL infusion of IV NEPA (plus matching oral placebo) or
 - a single capsule of oral NEPA (plus matching IV placebo)
- IV NEPA was initiated 30 minutes prior to chemotherapy and completed before starting AC administration; oral NEPA was taken 60 minutes prior to chemotherapy.
- Open-label oral dexamethasone (DEX) 12 mg was given to all patients 30 minutes before AC on Day 1 only.
- For subsequent cycles, patients received the same study treatment they were randomized to in Cycle 1.

Key inclusion criteria

- Females ≥ 18 years old with histologically or cytologically confirmed breast cancer, including recurrent or metastatic
- Naïve to moderately (MEC) or highly emetogenic chemotherapy (HEC) at study entry and scheduled to receive at least 4 consecutive cycles of an AC-based chemotherapy regimen
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Key Exclusion Criteria

- Scheduled to receive: (i) MEC or HEC any time beyond 6 hours post-AC initiation on Day 1 up to Day 1 of the subsequent cycle, (ii) radiotherapy to the abdomen or pelvis within 1 week prior to Day 1 or between Days 1 and 5 or (iii) a bone marrow or stem-cell transplant during the study
- Receipt of any drug with potential antiemetic efficacy within 24 hours or any systemic corticosteroid within 72 hours before start of AC
- Experienced any vomiting, retching, or at least mild nausea within 24 hours before start of AC
- Use of strong/moderate CYP3A4 inhibitors within 1 week or any CYP3A4 inducers within 4 weeks prior to Day 1 or during Days 1-5

Safety Assessments

- Safety was assessed primarily by treatment-emergent AEs (i.e., those occurring after the first dose of study treatment).
- Infusion site AEs were of special interest. All MedDRA preferred terms containing any of the following words: pain, erythema, swelling, urticaria, extravasation, thrombosis, phlebitis, discoloration, inflammation, induration, scar, pruritus, warmth, burning, catheter site-related reaction, were selected as potentially reflecting infusion-site events. These MedDRA preferred terms were then reviewed in a blinded fashion.

Efficacy Assessments

- From the start of chemotherapy on Day 1 through Day 5 (0-120h), each patient completed a diary, capturing emetic episodes, severity of nausea and rescue medications intake.
- Severity of nausea was evaluated daily using a 100-mm horizontal visual analog scale (VAS). The left end of the scale (0 mm) was labeled as 'no nausea' and the right end of the scale (100 mm) was labeled 'nausea as bad as it could be'.
- Efficacy endpoints included complete response (CR: no emesis, no rescue medication), no emesis, no use of rescue medication, and no significant nausea (NSN: maximum VAS score <25 mm).
- Patients also completed the Functional Living Index-Emesis (FLIE) questionnaire assessing the impact of CINV on important aspects of daily living during 0-120 hours of Cycles 1 and 2.

Statistical Analysis

- Four hundred patients stratified by region (US; non-US) and age class (< 55 years; ≥ 55 years) were to be randomized 1:1 to receive either IV NEPA or oral NEPA. Although no formal comparisons between treatment groups were planned, the inclusion of the oral NEPA control group was intended to help interpret any unexpected safety finding in the IV NEPA group.
- Demographics and baseline characteristics were summarized by treatment group using descriptive statistics.

- Treatment-emergent AEs and the AEs of special interest [i.e., infusion-site AEs] were summarized by frequency tables.
- For efficacy endpoints, percentages (including 95% confidence interval [CI] using the Wilson score method) of patients with CR, no emetic episodes, no rescue use, and with NSN were descriptively summarized by treatment for the acute (0-24 hours), delayed (25-120 hours) and overall (0-120 hours) phases. Differences between groups in response rate and 95% CI for the difference were calculated using the stratum-adjusted Cochran-Mantel-Haenszel (CMH) method for the risk difference. The percentage (including 95% CI) of patients with no impact on daily life (overall and by nausea and vomiting domains) based on FLIE, were also summarized by treatment.
- The Safety population included all patients who received active study drug (either IV NEPA, including partial infusion, or oral NEPA); the Full Analysis Population (FAS) included all patients who were randomized, received active study drug and received AC.

RESULTS

Patients and Baseline Characteristics

- A total of 402 patients were included in the safety population for a total of 1301 exposures in the study (641 infusions of IV NEPA and 660 capsules of oral NEPA).
- Almost all patients (97%) completed Cycle 1.
- The majority of patients (79% at Cycle 1 and similar percentages in subsequent cycles) received IV NEPA/placebo via a peripheral line.
- Baseline characteristics were similar in the two treatment groups (Table 1).

Table 1. Patient Baseline and Disease Characteristics (Safety Population)		
Characteristic	IV NEPA (N = 200)	Oral NEPA (N = 202)
Female	200 (100%)	202 (100%)
Fertility status		
Child-bearing potential	59 (29.5%)	52 (25.7%)
Post-menopausal/surgically sterile	141 (70.5%)	150 (74.3%)
Age (years), Mean (SD)	55.6 (9.94)	55.2 (9.73)
Race		
White	189 (94.5%)	186 (92.1%)
African American	4 (2.0%)	9 (4.5%)
Other	7 (3.5%)	7 (3.5%)
ECOG Performance Status ^a		
0	150 (76.5%)	148 (74.0%)
1	46 (23.5%)	52 (26.0%)
Extent of Cancer		
Localized	80 (40.0%)	74 (36.6%)
Locally advanced	94 (47.0%)	97 (48.0%)
Metastatic	26 (13.0%)	31 (15.3%)
AC Regimens		
Cyclophosphamide + epirubicin	114 (57.0%)	128 (63.4%)
Cyclophosphamide + doxorubicin	86 (43.0%)	74 (36.6%)

^a 4 IV NEPA and 2 oral NEPA patients had missing ECOG performance status

Adverse Events

- The overall incidence and intensity of treatment-emergent AEs were similar between the two treatment groups in Cycle 1 and throughout the entire study (Table 2).

Table 2. Summary of Treatment-Emergent Adverse Events in Cycle 1 and Throughout the Study (Safety population)				
Number (%) patients with	Cycle 1		Entire Study	
	IV NEPA N = 200 (%)	Oral NEPA N = 202 (%)	IV NEPA N = 200 (%)	Oral NEPA N = 203* (%)
At least one treatment-emergent adverse event (TEAE)	121 (60.5)	122 (60.4)	184 (92.0)	187 (92.1)
Severe (Grade ≥3) TEAEs	11 (5.5)	10 (5.0)	37 (18.5)	29 (14.3)
Serious TEAE	2 (1.0)	1 (0.5)	5 (2.5)	4 (2.0)
Any treatment-related adverse event (TRAЕ)	13 (6.5)	12 (5.9)	16 (8.0)	22 (10.8)
Severe (Grade ≥3) TRAЕ	0	0	1 (0.5)	2 (1.0)
Serious TRAЕ	0	0	0	1 (0.5)
Any TEAE leading to discontinuation	0	0	1 (0.5)	0
Any TRAЕ leading to discontinuation	0	0	0	0
Any TEAE resulting in death	0	0	0	0
Any infusion-site TEAE	2 (1.0)	0	3 (1.5)	9 (4.4)
Any treatment-related infusion site TEAE	0	0	0	0

^a one patient in the IV group received IV NEPA in cycles 1, 3 and 4 and, by mistake, oral NEPA in cycle 2 so is counted in each treatment group; TEAE: any treatment-emergent AE; TRAЕ: any TEAE deemed possibly, probably, or definitely related to study drug

- The most frequently reported treatment-emergent AEs were consistent with those expected for cancer patients undergoing AC-based chemotherapy; similar incidence rates were seen for IV NEPA and oral NEPA (Table 3). The most frequently reported severe treatment-emergent AEs are also summarized in Table 3.

Table 3. Treatment-Emergent All Grade ^a Adverse Events and Severe (Grade ≥3) ^a Adverse Events in Either Treatment Group throughout the Study (Safety population)				
Number (%) patients with	All Grade TEAEs ≥5%		Grade ≥3 TEAEs ≥2%	
	IV NEPA N = 200 (%)	Oral NEPA N = 203* (%)	IV NEPA N = 200 (%)	Oral NEPA N = 203* (%)
Alopecia	141 (70.5)	133 (65.5)	-	-
Leukopenia	40 (20.0)	33 (16.3)	13 (6.5)	7 (3.4)
Fatigue	30 (15.0)	34 (16.7)	-	-
Anemia	31 (15.5)	24 (11.8)	4 (2.0)	2 (1.0)
Neutropenia	25 (12.5)	24 (11.8)	11 (5.5)	9 (4.4)
Asthenia	27 (13.5)	17 (8.4)	-	-
Nausea	14 (7.0)	9 (4.4)	-	-
Headache	10 (5.0)	12 (5.9)	-	-
Diarrhea	10 (5.0)	9 (4.4)	-	-
Gamma-glutamyltransferase increased	11 (5.5)	7 (3.4)	-	-

^a Grade based on Common Terminology Criteria for Adverse Events (CTCAE V4.03); ^{*} one patient in the IV group received IV NEPA in cycles 1, 3 and 4 and, by mistake, oral NEPA in cycle 2 so is counted in each treatment group; TEAE: any treatment-emergent adverse event; "-": incidence < 2.0%

- The most common treatment-related AEs during the entire study were headache (2.5% IV NEPA, 3.4% oral NEPA), dizziness (2.5% in both groups), fatigue (2.0% in both groups) and constipation (2.5% IV NEPA, 1.0% oral NEPA); all other treatment-related AEs occurred in <2% of patients.
- There were no serious treatment-related AEs associated with IV NEPA; one serious treatment-related event was reported in the oral NEPA group (atrial fibrillation, occurring 9 days after oral NEPA administration in Cycle 4).
- No patient died on study and no treatment-related AEs led to study discontinuation in either treatment group.

Infusion-site Adverse Events/Hypersensitivity Reactions

- The review of infusion-site specific MedDRA preferred terms for the entire study revealed only 3 (1.5%) treatment-emergent AEs for IV NEPA patients; none of these AEs were deemed by the investigator to be related to IV NEPA infusion. By comparison, there were 9 (4.4%) infusion-site AEs in the oral NEPA (IV placebo infusion) treatment group.
- There were no infusion-site, hypersensitivity or anaphylaxis-like AEs reported as treatment-related in either treatment group.

Efficacy

- Complete response (Figure 1), no emesis, no use of rescue medication, and NSN rates (Table 5) were similar between treatment groups during Cycle 1.

Table 5. No Emesis, No Use of Rescue Medication and No Significant Nausea Rates during the Acute, Delayed and Overall Phases of Cycle 1 (FAS)						
	No Emesis		No Rescue Medication		No Significant Nausea	
% Patients	IV NEPA	Oral NEPA	IV NEPA	Oral NEPA	IV NEPA	Oral NEPA
Acute (0-24 h)	90.0%	92.6%	92.5%	94.6%	84.0%	85.1%
Delayed (25-120 h)	85.0%	87.1%	83.5%	87.6%	72.5%	77.2%
Overall (0-120 h)	82.5%	86.1%	81.5%	86.6%	70.0%	74.8%

- As measured by the FLIE, similar proportions of IV and oral NEPA patients reported no impact occurring on Day 1 due to nausea (nausea domain), due to vomiting (vomiting domain) or both (overall FLIE) (Figure 2).

CONCLUSIONS

- The adverse event profiles were consistent with that expected for breast cancer patients receiving AC and with that expected for the NK₁RA and 5-HT₃RA classes.
- Given the reports of hypersensitivity reactions and infusion-site AEs associated with the other NK₁RAs, it is reassuring that in this study there were no infusion-site AEs during any cycle (n = 641 infusions) deemed to be related to IV NEPA and no reports of hypersensitivity or anaphylaxis. This is likely due to the unique chemical characteristics of fosnetupitant and simplified formulation of IV NEPA not requiring surfactants, emulsifiers, solubility enhancers or allergenic excipients.
- The efficacy of IV NEPA was similar to that of oral NEPA, with high response rates in Cycle 1 across all efficacy endpoints, including the patient-reported FLIE.
- As a fixed single-dose prophylactic antiemetic combination given with DEX prior to AC, NEPA delivers guideline-recommended treatment, thereby minimizing the complexity of multi-agent dosing and complex decision-making.
- In this study, IV NEPA was safe and highly effective in breast cancer patients receiving multiple cycles of AC. Data also suggest a potential safety advantage over other NK₁RA regimens with regard to the lack of associated hypersensitivity and injection-site reactions.

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