Efficacy of Intravenous and Oral NEPA, a Fixed NK₁/5-HT₃ Receptor Antagonist Combination, in the Prevention of Highly Emetogenic Chemotherapy (HEC)-Induced Nausea and Vomiting (CINV)

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BACKGROUND

- With the introduction of the neurokinin-1 receptor antagonists (NK₁ RAs), combination antiemetic regimens have become the standard of care for prevention of chemotherapy-induced nausea and vomiting (CINV).
- In patients receiving highly emetogenic chemotherapy (HEC) the prophylactic triplet combination of an NK₁ RA + 5-HT₃ RA + dexamethasone (DEX) is guideline-recommended.¹ Utilizing this regimen, CINV can be prevented in the majority of patients (**Table 1**) during the 5 days following HEC administration.

Table 1. Overall (0-120 h) Complete Response (No Emesis, No Rescue) Rates for Aprepitant, Fosaprepitant and Rolapitant from Phase 3 Cisplatin-based HEC Studies			
	Oral Aprepitant Regimen	IV Fosaprepitant Regimen	Oral Rolapitant Regimen
Hesketh, et al J Clin Oncol 2003 ²	72.7%		
Poli-Bigelli et al Cancer 2003 ³	62.7%		
Schmoll et al Ann Oncol 2006 ⁴	72.0%		
Grunberg et al J Clin Oncol 2011 ⁵	72.3%	71.9%	
Rapoport et al Lancet Oncol 2015 - HEC 1 ⁶			70.0%
Rapoport et al Lancet Oncol 2015 - HEC 2 ⁶			68.0%

- The approval of oral NEPA, the first and only fixed antiemetic combination, comprised of the NK₁RA netupitant (300 mg) and 5-HT₃RA palonosetron (PALO, 0.50 mg), was based on studies demonstrating that a single oral NEPA capsule plus DEX given prior to cisplatin- and anthracycline/cyclophosphamide (AC)-based chemotherapy demonstrated superior prevention of CINV over PALO plus DEX for 5 days post-chemotherapy.^{7,8}
- As is the case with the other NK₁ RAs in the class, an intravenous formulation of NEPA (fosnetupitant 235 mg plus PALO 0.25 mg) was subsequently developed to offer additional options and convenience for healthcare providers and patients. In contrast to other IV NK₁ RAs, fosnetupitant does not require any surfactant, emulsifier or solubility enhancer to get a clear injectable solution. The formulation of IV NEPA has been simplified reducing the number of excipients and associated toxicities.
- In addition to showing pharmacokinetic bioequivalence of fosnetupitant and netupitant, a Phase 3 safety study demonstrated comparable safety profiles for IV NEPA and oral NEPA over initial and repeated cycles of HEC.⁹ These studies formed the basis of the recent approval of IV NEPA by the Food & Drug Administration.¹⁰
- This post-hoc analysis presents the efficacy of IV NEPA from the Phase 3 registration trial in the context of the oral NEPA results from the same study and also from the pivotal HEC studies in the oral NEPA registration program.

OBJECTIVES

- The objective of this post-hoc analysis was to summarize the efficacy of IV NEPA from the pivotal registration HEC trial relative to the efficacy of oral NEPA in patients receiving predominantly cisplatin-based HEC from individual and pooled pivotal trials.

METHODS

Study Designs

- All studies were multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group registration studies in adult chemotherapy-naïve patients.
- This post-hoc analysis focuses solely on the IV NEPA and oral NEPA results from these comparative studies. As Study 3 recruited patients receiving both HEC and moderately emetogenic chemotherapy (MEC), this analysis evaluates only those patients receiving HEC.
- In the IV NEPA study (Study 1), patients received IV NEPA as a 30-min infusion 30 minutes prior to HEC on Day 1. For oral NEPA (Studies 1-4), patients received a single capsule of oral NEPA 60 min prior to HEC on Day 1. In all studies, all patients also received oral DEX, 12 mg 30 min prior to HEC on Day 1 (just prior to IV NEPA in those patients) and 8 mg on Days 2-4.
- As netupitant is a CYP3A4 inhibitor, the dose of DEX was reduced for both IV and oral NEPA due to similar increased exposure to DEX when co-administered with both netupitant and fosnetupitant.

REFERENCES

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Key Inclusion Criteria

- Key inclusion criteria were the same for all four studies.
- Adults ≥18 years, diagnosed with a malignant tumor, with ECOG performance status 0, 1, or 2 (Studies 1, 3, and 4), or Karnofsky Index ≥70% (Study 2) and naïve to chemotherapy.
- Scheduled to receive cisplatin ≥50 mg/m² or another HEC agent, alone or in combination with other chemotherapy agents on Day 1.

Key Exclusion Criteria

- Key exclusion criteria were the same for all four studies.
- Scheduled to receive: (i) MEC or HEC from days 2-5 following HEC, (ii) moderately or highly emetogenic radiotherapy within 1 week prior to Day 1 or between Days 1 and 5, or (iii) a bone marrow or stem-cell transplant
- Receipt of any drug with potential antiemetic efficacy within 24h before Day 1
- Experienced any vomiting, retching or mild nausea within 24h before Day 1
- History or predisposition to cardiac conduction abnormalities, except for incomplete right bundle branch block
- Severe cardiovascular diseases, including myocardial infarction, unstable angina pectoris, significant valvular or pericardial disease, history of ventricular tachycardia, symptomatic congestive heart failure New York Heart Association (NYHA) class III-IV, or severe uncontrolled arterial hypertension
- Receiving or scheduled to receive any CYP3A4 inducers within 4 weeks or substrates/inhibitors within 1 week prior to Day 1

Assessments & Statistical Analysis

- Efficacy**
  - Efficacy endpoints for this analysis included proportions of patients with 1) complete response (CR: no emetic episodes and no rescue medication) and 2) no emetic episodes during the overall phase (0-120h) following HEC
- Safety**
  - Safety was assessed by treatment-emergent (TEAEs) and treatment-related (TRAEs) adverse events. Overall AE findings are reported for each individual study.
  - In addition to presenting the efficacy results for oral NEPA in the individual studies, the results were pooled across the 4 studies. No formal statistical comparisons were done between IV NEPA and oral NEPA for this post-hoc analysis.

RESULTS

Baseline Characteristics

- Baseline characteristics, with the exception of race, were similar across studies and between IV NEPA and oral NEPA treatment groups (**Table 2**). Patients were predominantly white in Studies 1-3 and Asian in Study 4.
- Lung cancer was the most common type of cancer in all studies and ≥95% of patients received cisplatin in each study.
- While not tabulated, most patients had either an ECOG performance status of 0-1 (Study 2) or Karnofsky Index of 80%-100% (Studies 1, 3, and 4).

Table 2. Patient Baseline and Disease Characteristics					
Characteristic	IV NEPA	Oral NEPA			
	Study 1 N = 203	Study 1 N = 201	Study 2 N = 136	Study 3 N = 75	Study 4 N = 413
Sex					
Male	52.7%	53.2%	56.6%	61.3%	70.7%
Female	47.3%	46.8%	43.4%	38.7%	29.3%
Age (years), Mean	60.0	58.9	54.1	57.9	54.6
Race					
White	99.0%	99.5%	100%	88.0%	0%
Black	1.0%	0%	0%	0	0%
Asian	0%	0.5%	0%	12.0%	100%
Most Common (≥ 5%) Cancer Types					
Lung	56.7%	53.2%	25.7%	57.3%	61.5%
Ovarian	13.3%	10.9%	17.6%	2.7%	0.2%
Gastric	5.9%	6.0%	5.9%	2.7%	0.2%
Head & Neck	5.4%	5.5%	24.3%	9.3%	5.8%
Chemotherapy					
Cisplatin	96.6%	95.0%	100%	96%	99.8%
Cyclophosphamide	0.5%	1.0%	0%	0%	0%
Dacarbazine	3.0%	4.0%	0%	4%	0%

Efficacy

- The efficacy analyses included 203 patients who received IV NEPA in Study 1 and 823 patients who received oral NEPA in Studies 1-4 (N = 201, 135, 75, and 412, respectively).
- The overall CR rate was 76.8% for IV NEPA and 79.8% for oral NEPA for the pooled studies (**Figure 1**).

Figure 1. Overall (0-120 h) Complete Response Rates

- The no emesis rate was 84.2% for IV NEPA and 82.0% for oral NEPA for the pooled studies (**Figure 2**).

Figure 2. Overall (0-120 h) No Emesis Rates

Safety

- In general, the AE profile for IV NEPA was similar to oral NEPA in Study 1 and also to the oral NEPA profile in Studies 2 - 4 (**Table 3**).
- The most common treatment-related AEs were constipation in Study 1 (IV NEPA 4.9%, oral NEPA 5.5%), hiccups (oral NEPA 5.1%) in Study 2, constipation in Study 3 (oral NEPA 2.7%) and hiccups (oral NEPA 2.7%) and constipation (oral NEPA 8.0%) in Study 4.
- There were no infusion-site reactions considered by the investigators to be related to IV NEPA.

Table 3: Summary of Treatment-Emergent Adverse Events

	IV NEPA	Oral NEPA			
Number (%) patients with	Study 1 N = 203	Study 1 N = 201	Study 2 N = 136	Study 3 N = 75	Study 4 N = 413
At least one TEAE	120 (59.1%)	135 (67.2%)	68 (50.0%)	47 (62.7%)	240 (58.1%)
Severe TEAEs	50 (24.6%)	51 (25.4%)	8 (5.9%)	6 (8.0%)	36 (8.7%)
Serious TEAE	29 (14.3%)	21 (10.4%)	0	3 (4.0%)	20 (4.8%)
Any TRAE	18 (8.9%)	19 (9.5%)	21 (15.4%)	5 (6.7%)	76 (18.4%)
Serious TRAE	0	0	0	0	2 (0.5%)
Any TRAE leading to discontinuation	1 (0.5%)	0	0	0	1 (0.2%)
Any TRAE resulting in death	0	0	0	0	0

TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event

CONCLUSIONS

- The efficacy of IV NEPA was comparable to that for oral NEPA and compares favorably to aprepitant, fosaprepitant, and rolapitant pivotal HEC studies where overall CR rates ranged from 63%-73% (**Table 1**).
- Considering the infusion site reactions for fosaprepitant and IV rolapitant, it is noteworthy that no injection site reactions were considered related to IV NEPA over repeated cycles and no instance of anaphylaxis. The low incidence of these events may be attributable to the chemical characteristics of fosnetupitant and to a reduced number of excipients present in the IV NEPA formulation.
- Both IV and oral formulations of NEPA represent safe, effective, and convenient single-dose prophylactic antiemetics targeting two distinct CINV pathways, offering comparable options for clinicians and patients in different settings.

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