Phase 3 Study of NEPA, a Fixed Combination of Netupitant and Palonosetron, Versus an Aprepitant Regimen for Prevention of Chemotherapy-induced Nausea and Vomiting (CINV)

ASCO Annual Meeting
June 2-6, 2017

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BACKGROUND

- All evidence-based antiemetic guidelines consistently recommend co-administration of a triplet regimen of a 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist (RA), a neurokinin-1 (NK_1) RA and a corticosteroid[1] (such as dexamethasone [DEX]) for patients receiving highly emetogenic chemotherapy (HEC)[1-3].
- Despite evidence demonstrating that CINV control is optimized when guideline recommendations are followed[4-5], guidelines are often inadequately adhered to in clinical practice. This may, in part, be due to perceived complexity of some of the multimodal antiemetic regimens, as the NK_1RAs, 5-HT_3RAs and corticosteroid components each have differing doses/schedules from[1] 1-4 days post-chemotherapy initiation. Simpler, less frequent dosing regimens have been shown to result in better compliance across a variety of therapeutic classes[6].
- NEPA was developed as a fixed combination of the highly selective NK_1RA, netupitant (300 mg), and the clinically[7] and pharmacologically[8] distinct 5-HT_3RA, palonosetron (0.5mg). The simultaneous targeting of two critical antiemetic pathways, in unison with the single dose administration results in a convenient antiemetic offering long-lasting protection from CINV. An intravenous fixed combination of NEPA is currently under evaluation by the United States Food & Drug Administration (FDA).
- Pivotal clinical studies leading to registration of oral NEPA in the United States and Europe have demonstrated superiority of NEPA plus DEX over PALO plus DEX in preventing CINV during the acute (0-24h), delayed (25-120h), and overall (0-120h) phases following both cisplatin-[9-11] and anthracycline-cyclophosphamide (AC)-based chemotherapy[6,9]. In addition, NEPA was shown to be efficacious over multiple cycles in patients receiving either HEC or moderately emetogenic chemotherapy (MEC)[12].
- Thus far, none of the NK_1RAs have been compared to each other, as all registration studies were conducted with a 5-HT_3RA/DEX comparative control.
- As part of the registration process in China, the China FDA requested that NEPA demonstrate comparable efficacy/safety to the current local standard of care in the HEC setting, an oral aprepitant (APR) triplet regimen.

METHODS

OBJECTIVE

- The objective was to demonstrate non-inferiority of NEPA to an aprepitant/granisetron (APR/GRAN) regimen in preventing CINV in patients receiving cisplatin-based HEC.

STUDY DESIGN AND TREATMENT GROUPS

- This was a Phase 3, multicenter, randomized, double-blind/double-dummy, parallel group international study conducted in Asia.
- Patients were stratified by gender and randomly assigned (1:1) to receive either NEPA or APR/GRAN treatment **(Table 1)**.

Table 1. Treatment Groups

	NEPA Regimen		APR/GRAN Regimen		
	Oral NEPA	Oral DEX	Oral APR	IV GRAN	Oral DEX
Day 1	NETU 300 mg/ PALO 0.50 mg	12 mg	125 mg	3 mg	12 mg
Day 2		8 mg	80 mg		8 mg
Day 3		8 mg	80 mg		8 mg
Day 4		8 mg			8 mg

APR, aprepitant; **GRAN**, granisetron; **DEX**, dexamethasone; **NETU**, netupitant; **IV**, intravenous; **PALO**, palonosetron

- NEPA and APR were administered 60 min prior to chemotherapy on day 1, while GRAN and DEX were administered 30 min prior to chemotherapy on day 1. On days 2-3, APR was administered 24 and 48h after its administration on day 1. On days 2-4, DEX was administered 24, 48 and 72h after its administration on day 1.
- Due to increased exposure to DEX when co-administered with NETU and APR, both CYP3A4 inhibitors, the dose of DEX was reduced in both treatment arms.
- The 3 mg granisetron dose is the registered dose in China.

KEY INCLUSION CRITERIA

- Males or females ≥18 years, diagnosed with a malignant solid tumor, ECOG Performance Status of 0-2, and naïve to chemotherapy
- Scheduled to receive first course of cisplatin-based (≥ 50 mg/m²) chemotherapy (as monotherapy or in combination with other chemotherapy)

KEY EXCLUSION CRITERIA

- Scheduled to receive: (i) MEC or HEC from days 2–5 following cisplatin, (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
- No serious cardiovascular disease history or predisposition to cardiac conduction abnormalities with the exception of incomplete right bundle branch block
- Chronic use of select CYP3A4 inducers within 4 weeks or chronic use of a substrate or inhibitor within 1 week prior to day 1.

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 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'. No significant nausea (NSN) was defined as a maximum score <25 mm.
- The primary efficacy endpoint was complete response (CR: no emesis, no rescue medication) during the overall phase.
- Key secondary efficacy endpoints included no emesis, NSN, and no rescue use.

SAFETY ASSESSMENTS

- Safety was assessed primarily by treatment-emergent adverse events (TEAEs) but also by vital signs, physical examination, clinical laboratory tests, and ECGs.

STATISTICAL ANALYSIS

- For the primary endpoint, non-inferiority of NEPA and APR/GRAN was to be demonstrated if the lower limit of the confidence interval (CI; two-sided 95% CI significance level) for the difference between NEPA and APR/GRAN in proportion of patients with overall CR was greater than -10%. The risk difference and associated 95% CI were analyzed using the Cochran-Mantel-Haenszel (CMH) test using gender as a stratifying variable in the model.
- For secondary endpoints of CR during the acute/delayed phases and no emesis, NSN and no rescue use during all phases, statistical analyses utilized the same methods as the primary endpoint, without testing for non-inferiority.
- The number and proportion of patients who experienced TEAEs and treatment-related adverse events (TRAEs) was listed and summarized by treatment group.

RESULTS

BASELINE CHARACTERISTICS

- A total of 834 patients were randomized; 829 (413 NEPA/416 APR/GRAN) and 828 (412 NEPA/416 APR/GRAN) represented the safety and full analysis set (FAS)/efficacy populations, respectively.
- Baseline characteristics were similar between treatment groups **(Table 2)**.
- The population was predominantly males (71%) and lung cancer was the most common (58%) cancer type.

Table 2. Patient Baseline and Disease Characteristics (Safety Population)

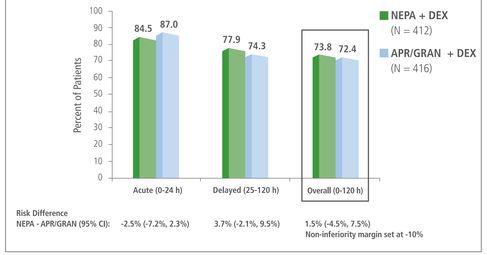
Characteristic	NEPA + DEX (N = 413)	APR/GRAN + DEX (N = 416)
Gender		
Male	**292** (70.7%)	**297** (71.4%)
Female	**121** (29.3%)	**119** (28.6%)
Age (years), Mean	**54.6**	**54.5**
Race		
Asian	**413** (100.0%)	**416** (100.0%)
ECOG Performance Status		
0	**175** (42.5%)	**171** (41.1%)
1	**231** (56.1%)	**236** (56.7%)
2	**7** (1.7%)	**9** (2.2%)
Most Common (≥ 5%) Cancer Types		
Lung	**254** (61.5%)	**229** (55.0%)
Head and neck	**24** (5.8%)	**31** (7.5%)
Cisplatin Dose (mg/m²), Median	**73**	**72**
Most Common (≥ 5%) Concomitant Chemotherapy		
Gemcitabine/Gemcitabine HCl	**123** (29.8%)	**93** (22.4%)
Pemetrexed/Pemetrexed Disodium	**69** (16.7%)	**79** (19.0%)
Docetaxel	**67** (16.2%)	**68** (16.3%)
Etoposide	**58** (14.0%)	**53** (12.7%)
Fluorouracil	**27** (6.5%)	**32** (7.7%)

APR, aprepitant; **GRAN**, granisetron; **SD**, standard deviation; **ECOG**, Eastern Cooperative Oncology Group; **DEX**, dexamethasone

EFFICACY

- For the primary efficacy endpoint, NEPA demonstrated non-inferiority to APR/GRAN **(Figure 1)**.

Figure 1. Complete Response Rates



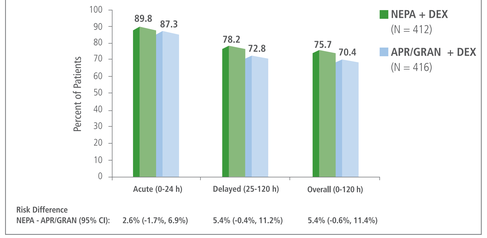
- No emesis and NSN rates were similar for NEPA and APR/GRAN in the acute phase and favored NEPA during the delayed and overall phases **(Table 3 and Figure 2)**. No rescue medication rates were significantly higher for NEPA during the delayed and overall phases **(Table 3)**.

Table 3. Secondary Endpoints: No Emesis, and No Rescue Medication Rates

Endpoint % Patients	NEPA + DEX (N = 412)	APR/GRAN + DEX (N = 416)	Risk Difference (95% CI)
No Emesis			
Acute	**85.2%**	**87.5%**	**-2.2%** (-6.9%, 2.4%)
Delayed	**79.4%**	**76.2%**	**3.3%** (-2.4%, 8.9%)
Overall	**75.0%**	**74.0%**	**1.1%** (-4.8%, 6.9%)
No Rescue Use			
Acute	**98.8%**	**98.3%**	**0.5%** (-1.2%, 2.1%)
Delayed	**97.6%**	**94.7%**	**2.9%** (0.2%, 5.5%)
Overall	**96.6%**	**93.5%**	**3.1%** (0.2%, 6.1%)

APR, aprepitant; **GRAN**, granisetron; **DEX**, dexamethasone

Figure 2. No Significant Nausea Rates



SAFETY

- The overall incidence of TEAEs were comparable between the two treatment groups **(Table 4)**.
- The most common TRAEs were constipation and hiccups.
- Among the patients reporting TEAEs, the majority (90%) reported events of mild/moderate intensity, with slightly more severe TEAEs in the APR/GRAN group.
- The proportion of patients with serious TEAEs was similar and low for NEPA and APR/GRAN.
- There were no deaths in the NEPA group, while 4 patients treated with APR/GRAN died due to unrelated TEAEs.
- Changes from baseline in 12-lead ECGs were rare and similar between treatment groups at each time point.

Table 4. Summary of Adverse Events

N (%) patients with	NEPA + DEX (N = 413)	APR/GRAN + DEX (N = 416)	Overall (N = 829)
At least one treatment-emergent adverse event (TEAE)	**240** (58.1%)	**239** (57.5%)	**479** (57.8%)
Severe TEAE	**36** (8.7%)	**45** (10.8%)	**81** (9.8%)
Any TRAE	**76** (18.4%)	**60** (14.4%)	**136** (16.4%)
Most common (≥2%) TRAE Constipation Hiccups	 **33** (8.0%) **11** (2.7%)	 **26** (6.3%) **6** (1.4%)	 **59** (7.1%) **17** (2.1%)
Serious TEAE	**20** (4.8%)	**19** (4.6%)	**39** (4.7%)
Serious treatment-related adverse event (TRAE)	**2** (0.5%)	**2** (0.5%)	**4** (0.5%)
Any TRAE leading to discontinuation	**1** (0.2%)	**0**	**1** (0.1%)
Any TEAE resulting in death	**0**	**4** (1.0%)[a]	**4** (0.5%)

[a] None of these were considered to be related to study treatment

CONCLUSIONS

- In this first head-to-head study comparing NK_1 RA-containing regimens, a single dose of NEPA was non-inferior to a standard 3-day APR/GRAN regimen (both in combination with DEX) for the primary endpoint of overall CR.
- For secondary efficacy endpoints of no emesis, NSN and no rescue medication use, rates were similar during the acute phase and favored NEPA during the delayed and overall phases, particularly for nausea control. This was in line with results observed in the NEPA pivotal registration trials.
- NEPA was well tolerated with a comparable adverse event profile to APR/GRAN. The majority of AEs were mild/moderate in intensity, unrelated to study treatment, and typical for a cancer population undergoing chemotherapy. There were no cardiac safety concerns for either treatment based on ECG assessments.
- As a combination antiemetic targeting two antiemetic pathways with a single dose administered only once per cycle, NEPA offers a convenient and simplified prophylactic antiemetic as compared to a 3-day aprepitant/granisetron regimen in patients receiving HEC.

ACKNOWLEDGEMENTS: The authors would like to thank the clinical investigators, patients and site personnel at each of the participating centers. Editorial and medical writing assistance was provided by Jennifer Vanden Burgt, Minneapolis, MN and funded by Helsinn Healthcare SA, Lugano, Switzerland. The trial was sponsored by Helsinn Healthcare SA.

REFERENCES

1. Hesketh PJ, et al. J Clin Oncol 2016;34(4):381-6. **2.** Roila F, et al. Ann Oncol 2016;27(5):v119-v133. **3.** National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Antiemesis [v1.2017]. https://www.nccn.org Accessed March 2017. **4.** Aapro M, et al. Ann Oncol. 2012;23(8):1986-1992. **5.** Gilmore JW, et al. J Oncol Pract 2014;10(1):68-74. **6.** Claxton AJ, et al. ClinTher 2001;23:1296–1310. **7.** Jordan K, et al. Ann Oncol 2015;26(6):1081-1090. **8.** Rojas C, et al. Eur J Pharmacol 2014; 722:26-37. **9.** Hesketh PJ, et al. Ann Oncol 2014;25:1340-6. **10.** Aapro M, et al. Ann Oncol 2014;25:1328-33. **11.** Aapro M, et al. Support Care Cancer 2017;25(4):1127-1135. **12.** Gralla RJ, et al. Ann Oncol 2014;25:1333-9.

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