Comparison Of Sustained Release Granisetron (APF530) To A Single Dose Of Palonosetron For The Prevention Of Chemotherapy-Induced Nausea And Vomiting (CINV) Following A Phase 3 Study

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Background

Prevention and control of nausea and emesis are paramount in the treatment of cancer patients. $5HT_3$ antagonists, as a class, have become the most common antiemetic agents used in chemotherapy induced nausea and vomiting (CINV). APF530 is a viscous tri(ethylene glycol) poly(ortho ester) (TEG-POE) based formulation that is delivered by a single subcutaneous injection in the abdomen and contains the $5HT_3$ antagonist, granisetron. APF530 is designed to deliver granisetron over a 5-day period.

Methodology

***Study Design*:** Phase 3, randomized, multicenter, observer-blind, double-dummy, parallel group study.

***Participants*:** Chemotherapy naïve or non-naïve, male or female patients, ≥18 years old. Patients were allowed to enroll and continue into subsequent treatment cycles regardless of the severity of nausea and/or vomiting in the previous chemotherapy cycle.

- Patients received single-day administrations of either moderately (MEC) or highly (HEC) emetogenic chemotherapy as defined by Hesketh et al, 1999[1].
- Study drug was given in up to four chemotherapy treatment cycles.
- Treatment cycles were separated by a period of at least 7 days and no more than 28 (+3) days.
- An analysis of plasma granisetron concentrations was performed in a subset of patients.

***Drug administration*:** The IV and SC injections were given concomitantly 30 to 60 minutes before chemotherapy. Placebo was isotonic saline for both the IV and SC injections.

Treatment groups:

- Palonosetron 0.25 mg IV and placebo SC
- Granisetron 5 mg SC and placebo IV (in study, but results not included)
- Granisetron 10 mg SC and placebo IV

Standardized doses of dexamethasone were required for all treatment cycles.

	MEC	HEC
Dexamethasone Day 1	8 mg IV	20 mg IV
Dexamethasone Days 2, 3, and 4	None	8 mg PO, BID

Primary Endpoints as defined by Complete Response (CR) (no emetic episodes and no use of rescue medication):

- Non-inferiority to palonosetron in prevention of acute (0 to 24 hours) onset CINV in MEC
- Non-inferiority to palonosetron in prevention of acute onset CINV in HEC
- Non-inferiority to palonosetron in prevention of delayed (24 to 120 hours) onset CINV in MEC
- Superiority to palonosetron in prevention of delayed onset CINV in HEC

***Outcome Measures*:** A daily diary was used to collect data pertaining to severity of nausea (mild, moderate or severe), vomiting/retching episodes and use of rescue medication over the 5 day treatment period. Non-inferiority was determined by the position of the lower bound of the exact confidence interval (CI) calculated using the difference in CR rate between APF530 and palonosetron in relation to the lower bound of the predefined 15% non-inferiority margin. Non-inferiority was declared if the lower bound of the CI was above 15%. Within each emetogenic stratum the type 1 error rate was adjusted for the 2 APF530 doses and 2 endpoints using Hochberg's Bonferroni procedure[2]. Treatment comparisons were based on Fisher's exact test.

[1] Hesketh PJ. Defining the emetogenicity of cancer chemotherapy regimens: relevance to clinical practice. The Oncologist 1999;4:191-196

[2] Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988; 75:800-802

Demographics

Overall, the C2006-01 clinical study enrolled a total of 1,395 patients. The total number of patients enrolled in the modified-intent to treat population for Cycle 1 in the MEC was 212 and 208, and in the HEC 240 and 238 in the 10 mg APF530 and palonosetron groups, respectively.

- Females were the majority of the treatment populations, for both the MEC (83.3-83.5%) and HEC (62.8-66.5%) Regimens.
- Breast, lung and ovarian were the most common types of cancer enrolled in both emetogenic strata.
- Mean age ranged from 55.1 to 58.1 @ treatment groups.
- Caucasians were the majority of the treatment populations, for both the MEC (56.4-66.5%) and HEC (60.5-62.4%) Regimens.

Efficacy Results

- **Figures 1 and 2** detail the efficacy results for CR in Cycle 1.
- The 10 mg dose of APF530 was shown to be non-inferior to palonosetron for the prevention of acute-onset (0-24 hours) and delayed-onset (20-120 hours) CINV following administration of MEC and HEC.
- Although superiority was not obtained for the delayed HEC, the 10 mg APF530 dose was comparable to the CR rates of palonosetron.
- The secondary efficacy analyses for Complete Control (CR with no more than mild nausea) and Total Response (CR with no nausea) during Cycle 1 were supportive of the primary analyses.
- **Figure 3** compares CR rates between chemo-naïve vs. non-naïve patients. For the non-naïve patients the 10 mg APF530 dose showed numerically higher CR rates than the palonosetron dose group. Generally, the 10 mg dose non-naïve patients performed better that the naïve patients.
- In **Figure 4**, the 10 mg APF530 dose is shown to be effective over initial and multiple treatment cycles with a tendency to increase over multiple cycles.

Figure 1
Cycle 1 Efficacy: Complete Response – Moderate Emetogenic Chemotherapy

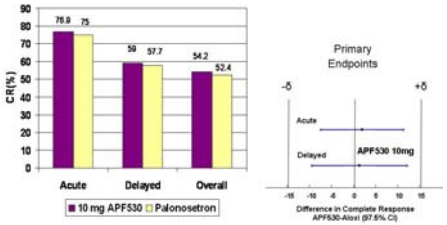


Figure 2
Cycle 1 Efficacy: Complete Response – Highly Emetogenic Chemotherapy

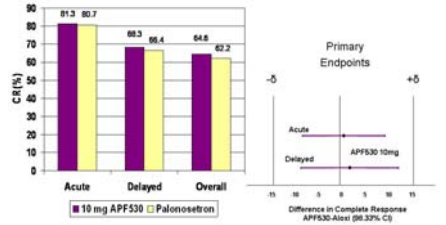


Figure 3
Summary of Complete Response in Cycle 1 Comparing Naïve vs Non-Naïve

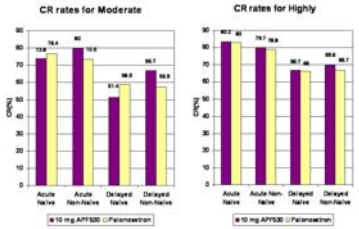
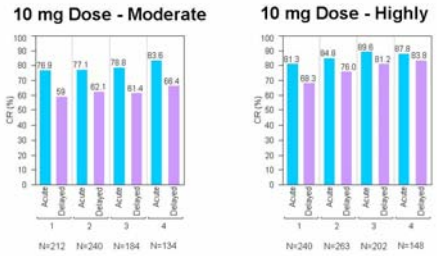


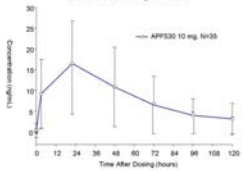
Figure 4
10 mg APF530 Complete Response in Cycles 1-4



PK Results

- **Figure 5**. After a single SC administration of 10 mg APF530, granisetron was absorbed with median Tmax values of 22.7 hours. Blood levels of granisetron were observed over the entire 5-day period.

Figure 5
Mean (± SD) plasma concentration of granisetron in patients receiving APF530



Safety Results

- Overall, <1% of the patients discontinued for treatment related events.
- AEs were generally mild in severity and considered by the investigator to be unrelated to treatment.
- **Figure 6** shows the most frequent treatment related AEs in Cycle 1.
- There were no significant differences in AEs (excluding injection site reactions) between APF530 and palonosetron.
- One SAE (pulmonary embolism) occurring 15 days after treatment was considered to be possibly related to APF530.
- There were no patient deaths due to treatment related AEs or SAEs.

Figure 6
Incidence of Treatment Related Adverse Events

System Organ Class	Preferred Term	Severity	10 mg APF530 N=468 (%)	IV Palonosetron N=463 (%)
Gastrointestinal Disorders	Constipation	Mild	3.2	2.6
		Moderate	0.9	0.4
		Severe	0.4	0
Central Nervous System	Headache	Mild	2.1	0.6
		Moderate	0.4	0.6
		Severe	0.2	0.6

- Injection site observations occurred in up to 15% of patients, including bruising, nodules, erythema, and pain.
- Related injection site reactions were mild in severity in Cycle 1, **Figure 7**.

Figure 7
Summary of Injection Site Observations Related to Treatment by Severity in Cycle 1

Observation	Severity	10 mg APF530 (N=468) n (%)	Saline (N=463) n (%)
Bruising	Mild	69 (14.7)	29 (6.3)
	Moderate	4 (0.9)	1 (0.2)
Nodule	Mild	42 (9.0)	3 (0.6)
	Moderate	2 (0.4)	0
Erythema	Mild	37 (7.9)	11 (2.4)
	Moderate	1 (0.2)	0
Pain	Mild	26 (5.6)	3 (0.6)
	Moderate	1 (0.2)	0

Conclusion

- Compared to palonosetron, patients receiving the 10 mg dose of APF530 had numerically higher CR rates for acute, delayed and overall CINV in patients undergoing either MEC or HEC.
- 10 mg APF530 was shown to be effective and well tolerated over initial and multiple treatment cycles.
- The safety profile for APF530 is similar to palonosetron as well as previously published profiles for granisetron.
- The NDA for the 10 mg dose of APF530 was submitted in May of 2009 and was accepted for review.
- PDUFA date is March 18, 2010.

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