Phase 3 Study Of Sustained Release Granisetron (APF530) Compared To Palonosetron For The Prevention Of Chemotherapy-Induced Nausea And Vomiting (CINV)

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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. 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: 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.

Three treatment groups were studied in Cycle 1:

- Palonosetron 0.25 mg IV and placebo SC
- 250 mg APF530 (5 mg granisetron) and placebo IV
- 500 mg APF530 (10 mg granisetron) and placebo IV

Two treatment groups were studied in Cycles 2-4:

- 250 mg APF530 (5 mg granisetron)
- 500 mg APF530 (10 mg granisetron)

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

Cycle 1
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 and superiority were declared if the lower bound of the CI was above 15% and 0%, respectively. 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

Figure 1 is a summary of the Demographic Characteristics in Cycle 1. A total of 1395 patients received study drug at 103 sites in 3 countries. The table below details the total number of patients enrolled in each cycle and stratum.

	MEC			HEC		
Population	APF530 5 mg	APF530 10 mg	palonosetron 0.25 mg	APF530 5 mg	APF530 10 mg	palonosetron 0.25 mg
Safety Cycle 1	220	218	215	244	250	256
mITT Cycle 1	214	212	208	229	240	238
PP Cycle 1	201	195	192	197	192	203
mITT Cycle 2, n	247	240	—	263	263	—
mITT Cycle 3, n	191	184	—	207	202	—
mITT Cycle 4, n	134	134	—	158	148	—

- Females were the majority of the treatment populations, with 1,040 females and 355 males enrolled.
- The mean age across the 3 treatment groups ranged from 54.8 to 58.1 years.
- Breast, lung and ovarian were the most common types of cancer enrolled in both emetogenic strata.

Figure 1
Summary of Demographic and Baseline Characteristics Cycle 1

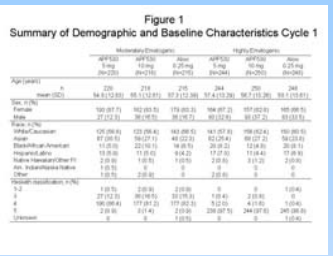


Figure 2
Cycle 1 Efficacy: Complete Response – Moderate Emetogenic Chemotherapy

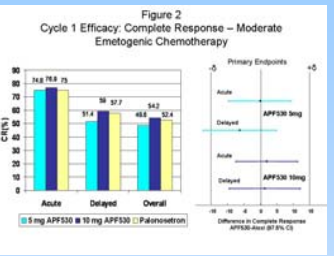


Figure 3
Cycle 1 Efficacy: Complete Response – Highly Emetogenic Chemotherapy

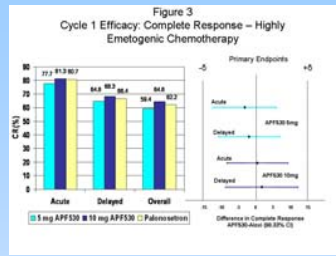


Figure 4
Summary of Complete Response in Cycle 1 by Chemotherapeutic Regimen

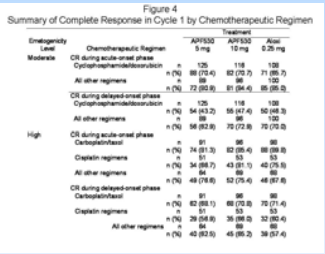


Figure 5
Summary of Complete Response in Cycle 1 Comparing Naïve vs Non-Naïve

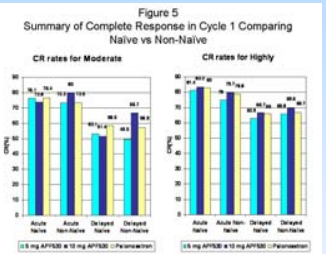


Figure 6
10 mg APF530 Complete Response in Cycles 1-4

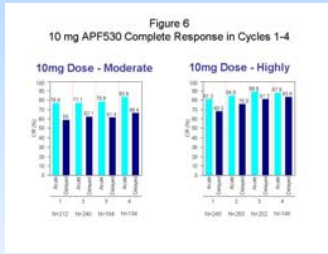


Figure 7
Mean (± SD) plasma concentration of granisetron in patients receiving APF530

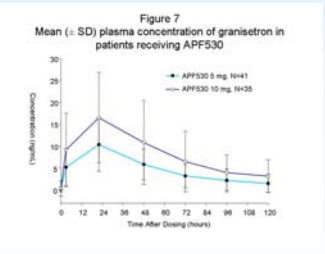
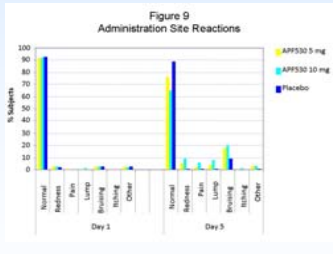


Figure 8
Treatment-Emergent Related Adverse Events in Cycle 1

	APF530 5 mg		APF530 10 mg		Aloxi 0.25 mg	
	N	%	N	%	N	%
Serious Adverse Events	1	0.2	0	0	0	0
Discontinued Due to Adverse Event	1	0.2	1	0.2	0	0
Frequent Adverse Events						
Gastrointestinal disorders						
➢Constipation	62	13.4	72	15.4	62	13.4
➢Nausea	56	12.1	60	12.8	41	8.9
➢Diarrhea	49	10.6	44	9.4	39	8.4
➢Abdominal pain	21	4.5	13	2.8	28	6.0
Nervous System						
➢Headache	31	6.7	47	10.0	45	9.7

Figure 9
Administration Site Reactions



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Efficacy Results

- **Figures 2 and 3** detail the efficacy results for CR in Cycle 1.
- The study was well balanced and statistically robust to accurately determine the primary endpoints:
  - Both the 5 mg and 10 mg doses of APF530 were shown to be non-inferior to palonosetron for the prevention of acute-onset (0-24 hours) CINV following administration of MEC and HEC.
  - The 10 mg APF530 dose was shown to be non-inferior to palonosetron for the prevention of delayed-onset (24-120 hours) CINV following administration of MEC.
  - Although superiority was not obtained for the delayed HEC, both doses of APF530 were 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 4** summarizes the CR rates for the most common chemotherapeutic regimens (cyclophosphamide / doxorubicin, carboplatin and cisplatin) that were utilized during the study in Cycle 1.
- **Figure 5** summarizes the CR rates in Cycle 1 and shows comparable 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 both the 5 mg APF530 and palonosetron dose groups.
- In **Figure 6**, the 10 mg APF530 dose is shown to be effective over initial and multiple treatment cycles with a tendency to increase over multiple cycles.
- No gender differences were noted for CR in acute CINV in either emetogenic strata. Generally, in the delayed phase males had higher CR rates than females.
- Generally, the older population (≥65 years) responded better than the younger population (<65 years) in all treatment groups.

PK Results

- **Figure 7**. After a single SC administration of 5 mg APF530 or 10 mg APF530, granisetron was absorbed with median Tmax values of 23.8 and 22.7 hours, respectively. Blood levels of granisetron were observed over the entire 5-day period.

Safety Results

- **Figure 8** details the most frequent treatment-emergent related AEs in Cycle 1, with constipation as the most common.
- Overall, <1% of the patients discontinued for treatment related events.
- AEs (excluding injection site reactions) were experienced by 67.6% to 67.9% of patients across treatment groups in Cycle 1.
- AEs were generally mild in severity and considered by the investigator to be unrelated to treatment.
- There were no significant differences in AEs (excluding injection site reactions) between APF530 and palonosetron.
- Changes in laboratory parameters were reflective of the patients' underlying disease state and chemotherapeutic regimens.
- Among the most frequently reported SAEs febrile neutropenia, anemia, and neutropenia were consistent with cancer chemotherapy and none were considered to be related to study drug.
- 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 9** details the protocol mandated injection site observations that were recorded on Days 1 and 5.
- Injection site reactions occurred in up to 20% of patients, including bruising, nodules, erythema, and pain.
- Most injection site reactions were mild (>87%) in severity in any treatment group in Cycle 1 and Cycles 2-4.
- The majority of injection site reactions diminished over multiple treatment cycles or by the final follow-up visit.

Conclusion

- 3 out of the 4 primary endpoints were met for the study with the 10 mg APF530 dose.
- 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.
- APF530 was shown to be effective and well tolerated over initial and multiple treatment cycles.
- 1,043 patients went on to receive a total of 2,347 doses of APF530 in Cycles 2-4. Only 2 of these patients (<0.2%) discontinued therapy due to treatment related AEs.
- The safety profile for APF530 is similar to palonosetron as well as previously published profiles for granisetron.
- ECG testing indicated that APF530 and palonosetron had similar effects on ECG parameters and did not appear to cause adverse cardiovascular events.
- The NDA for the 10 mg dose of APF530 was submitted in May of 2009.

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