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. 5-HT3 receptor antagonists, such as aprepitant, ondansetron, and granisetron, are standard of care for the prevention of chemotherapy-induced nausea and vomiting (CINV). A new sustained-release formulation of granisetron (APF530) is designed to deliver granisetron over a 5 day period.

Methodology
Study Design: Randomized, evaluator-blinded, double-blind, placebo group study.
Participants: The study included patients who underwent chemotherapy for a period of at least 7 days and no more than 28 (+3) days. Treatment cycles were separated by a period of at least 7 days and no more than 28 (+3) days. A total of 3 sites in 3 countries participated.

Efficacy Results
Figure 2 and 3 depict non-inferiority results for CR in Cycle 1.

The study was well-tolerated and statistically robust to accurately determine the primary endpoint:
- Both the 5 mg and 10 mg doses of APF530 were shown to be non-inferior to palonosetron for the prevention of acute (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 (24-120 hours) CINV following administration of MEC.
- Although non-inferiority was not determined for the 5 mg dose, both doses of APF530 were comparable to the CR rates of palonosetron.

The primary efficacy analyses for Complete Control (CR with no more than mild nausea) and Total Response (CR with no rescue medication) during Cycle 1 were supportive of the primary analysis.

Figure 4 summarizes the ORR in Cycle 1 and shows comparable CR rates between males vs. females, races, and age patients.

For the non-naïve patients the 10 mg APF530 dose showed numerically higher CR rates than both the 5 mg APF530 and palonosetron.

Figure 5 shows the ORR in Cycle 2 and reflects the non-naïve patients vs. naïve patients. The 10 mg APF530 dose showed numerically higher ORRs than both the 5 mg APF530 and palonosetron.

No gender differences were noted for CR in acute CINV in other emetogenic strata. Generally, the delayed phase results reflected similar CR rates between males and females.

Generally, the older population (65 years) responded better than the younger population (<65 years) at all treatment groups.

Safety Results
Figure 6 depicts the most frequent treatment-related emergent AEs. APF530 was associated with restlessness (Table 1) as the most common.

In Cycle 1, <1% of patients discontinued due to treatment-related events.

AEs including injection site reactions were experienced by 0.3% to 0.7% of patients across treatment groups in Cycle 1.

There were no significant differences in AEs (excluding injection site reactions) between APF530 and palonosetron.

No changes in laboratory parameters were reflective of the patients undergoing disease state and chemotherapy regimens.

Among the most frequently reported SAEs were febrile neutropenia, anemia, and neutropenia were consistent with cancer disease state.

AEs were generally mild in severity and considered by the investigator to be unrelated to treatment.

The NDA for the 10 mg dose of APF530 was submitted in May of 2009.

The safety profile for APF530 is similar to palonosetron as well as previously published profiles for granisetron.

No serious injection site reactions were reported above the common injection site reactions reported with granisetron.

The majority of injection site reactions resolved over multiple treatment cycles or by the final follow-up visit.

Conclusion
The 10 mg oral APF530 dose was non-inferior 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 overall and multiple treatment cycles.

Life-table analysis of patients remaining with CR was a measure of days on APF530 in Cycle 4. Using a log rank test, patients with CR had a significantly longer time on APF530 than patients without CR.

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 clinically significant changes in ECG parameters.

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