San Antonio Breast Cancer Symposium, December 8-12, 2015

PI-10-07

Phase 3 Comparison of APF530 Versus Ondansetron, Each in a Guideline-Recommended 3-Drug Regimen, for Prevention of Chemotherapy-Induced Nausea and Vomiting Due To Anthracycline + Cyclophosphamide–Based Highly Emetogenic Chemotherapy Regimens: a Post Hoc Subgroup Analysis of the MAGIC Trial

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BACKGROUND

- Chemotherapy-induced nausea and vomiting (CINV) associated with highly emetogenic chemotherapy (HEC) adversely affects patient quality of life, especially in the delayed phase (24-120 h after chemotherapy), and affects chemotherapy compliance[1]
- Anthracycline + cyclophosphamide (AC)–based regimens, considered among the most difficult to manage, were reclassified from moderately emetogenic chemotherapy (MEC) to HEC in American Society of Clinical Oncology (ASCO) 2011 emetogenicity guidelines[2]
- AC-based HEC is often administered to breast cancer patients, a mostly female population with a high risk for CINV[3]
- Antiemesis guidelines for HEC recommend a 3-drug regimen of a 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist, a neurokinin 1 (NK-1) receptor antagonist, and a corticosteroid[2,4]

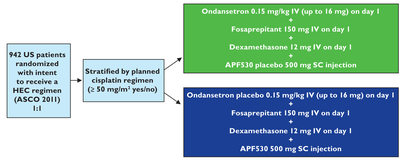
APF530 (granisetron injection, extended release)

- APF530 is a new formulation of 2% granisetron and a viscous bioerodible tri(ethylene glycol) poly(orthoester) polymer that undergoes controlled hydrolysis in subcutaneous (SC) tissue to provide extended release of granisetron for the prevention of both acute (0-24 h after chemotherapy) and delayed CINV
- A single SC dose of APF530 provides therapeutic concentrations of granisetron for ≥ 5 days[5]
- In the phase 3 Modified Absorption of Granisetron In the prevention of CINV (MAGIC) trial, APF530 demonstrated superior complete response (CR; no emesis and no rescue medication use) in delayed CINV with HEC, compared with ondansetron (64.7% vs 56.6%; *P* = 0.014; 8% absolute improvement), each with an NK-1 antagonist and dexamethasone (DEX) (NCT02106494)[6]
  - APF530 is the first and only 5-HT_3 antagonist to demonstrate superiority over another in a 3-drug versus 3-drug comparison phase 3 efficacy trial
- This post hoc analysis evaluated the efficacy and safety of APF530 in patients receiving an AC-based HEC regimen

METHODS

- This was a prospective, randomized, double-blind, double-dummy, multicenter phase 3 trial (**Figure 1**)
- A total of 942 adult patients in the United States with histologically or cytologically confirmed malignancy and scheduled to receive single-day HEC (according to ASCO 2011 emetogenicity criteria) were enrolled
- Patients were stratified by planned cisplatin ≥ 50 mg/m² (yes/no) and randomized 1:1 to receive APF530 500 mg SC (granisetron 10 mg) or ondansetron 0.15 mg/kg IV
- Patients were scheduled to receive concomitant DEX 12 mg IV and fosaprepitant 150 mg IV on day 1 and oral DEX 8 mg once daily on day 2 and 8 mg twice daily on days 3 and 4
- Rescue medication was permitted at the investigator's discretion

Figure 1. MAGIC Trial Design



ASCO = American Society of Clinical Oncology; HEC = highly emetogenic chemotherapy.

Primary and Secondary End Points

- The primary end point was CR in the delayed phase
- Secondary and other end points included
  - CR in acute and overall (0-120 h) phases
  - Complete control (CC; CR and no more than mild nausea) and total response (TR; CR and no nausea) in acute, delayed, and overall phases
- Rates were compared using 95% confidence intervals (CIs) for treatment differences using a modified intent-to-treat (mITT) population (all patients who received HEC and study drug and had at least 1 postbaseline efficacy measure)
- Safety assessments included treatment-emergent adverse events (TEAEs), injection-site reactions (ISRs), laboratory parameters, and vital signs using the safety population (all patients who received study drug)

Post Hoc Analysis of AC Regimens

- A post hoc analysis was conducted on the subgroup of patients who received an AC-containing HEC regimen
- This analysis was not powered to detect treatment differences

RESULTS

Patient Population

- A total of 589/902 patients (65%) in the mITT population received AC-based HEC (APF530 arm, n = 291; ondansetron arm, n = 298)
- Baseline demographics were balanced between treatment arms (**Table 1**)
- The majority of patients in the AC subgroup were white, female, and had an Eastern Cooperative Oncology Group performance status of 0
- The most common AC-based chemotherapy regimen in both treatment arms was cyclophosphamide < 1500 mg/m² + doxorubicin (APF530 arm, 87.3%; ondansetron arm, 89.3%)

Table 1. Patient Demographics and Baseline Clinical Characteristics (AC Subgroup, mITT Population)

	APF530 Arm N = 291	Ondansetron Arm N = 298
Age, mean (SD), y	54.1 (10.6)	53.8 (10.9)
Female, n (%)	289 (99.3)	293 (98.3)
Ethnicity, n (%)		
Not Hispanic/Latino	231 (79.4)	242 (81.2)
Hispanic/Latino/other	60 (20.6)	56 (18.8)
Race, white, n (%)	233 (80.1)	232 (77.9)
Body mass index (kg/m²)		
n	283	290
Mean (SD)	30.3 (6.9)	30.2 (6.9)
ECOG PS, n (%)		
0	244 (83.8)	238 (79.9)
1	46 (15.8)	58 (19.5)
Unknown	1 (0.3)	2 (0.7)
Currently drink alcohol, n (%)		
Any	111 (38.1)	110 (36.9)
≥ 8 drinks/wk	5 (1.7)	5 (1.7)
Currently smoke tobacco, n (%)	34 (11.7)	34 (11.4)

AC = anthracycline + cyclophosphamide; ECOG PS = Eastern Cooperative Oncology Group performance status; mITT = modified intent-to-treat; SD = standard deviation.

Efficacy

- In the AC subgroup (**Table 2**), delayed-phase CR was numerically higher in the APF530 arm versus the ondansetron arm, approaching significance (APF530 arm, 63.6%; ondansetron arm, 56.0%; *P* = 0.062)
  - In the overall phase, trends in favor of the APF530 arm versus the ondansetron arm were observed, although not statistically significant
  - As expected, no appreciable benefit in the APF530 arm compared with the ondansetron arm was observed in the acute phase
- There were numerically higher, although not statistically significantly so, delayed- and overall-phase CC and TR rates in the APF530 arm versus the ondansetron arm, 2 more stringent end points that measure additional effect on nausea

Table 2. Complete Response, Complete Control, and Total Response During Delayed, Overall, and Acute CINV (AC Subgroup, mITT Population)

Response and Phase, n (%)	APF530 Arm N = 291	Ondansetron Arm N = 298	Treatment Difference (95% CI), % (APF530 – Ondansetron)
Complete response			
Delayed	185 (63.6)*	167 (56.0)	7.5 (-0.4, 15.4)
Overall	163 (56.0)	153 (51.3)	4.7 (-3.4, 12.7)
Acute	205 (70.4)	204 (68.5)	2.0 (-5.4, 9.4)
Complete control			
Delayed	171 (58.8)	156 (52.3)	6.4 (-1.6, 14.4)
Overall	149 (51.2)	143 (48.0)	3.2 (-4.9, 11.3)
Acute	193 (66.3)	191 (64.1)	2.2 (-5.5, 9.9)
Total response			
Delayed	119 (40.9)	107 (35.9)	5.0 (-2.9, 12.8)
Overall	100 (34.4)	94 (31.5)	2.8 (-4.8, 10.4)
Acute	164 (56.4)	173 (58.1)	-1.7 (-9.7, 6.3)

*P = 0.062 versus ondansetron arm.
AC = anthracycline + cyclophosphamide; CINV = chemotherapy-induced nausea and vomiting; mITT = modified intent-to-treat.

Safety

- Consistent with the overall population, the APF530 regimen was generally well tolerated in this AC subgroup; no new safety signals were identified (**Table 3**)
- Most patients experienced at least 1 TEAE (APF530 arm, 93.5%; ondansetron arm, 91.1%)
- Excluding ISRs, the most frequently reported TEAEs were fatigue, constipation, nausea, and headache, occurring with a similar frequency in each treatment arm
  - The most common treatment-related TEAEs in the APF530 and ondansetron arms were constipation (8.2% vs 5.9%, respectively) and headache (7.2% vs 5.9%)
- 4.1% of patients in the APF530 arm and 2.0% of patients in the ondansetron arm experienced serious TEAEs; no TEAEs led to death
- 0.3% and 0.3% of patients in the APF530 and ondansetron arms, respectively, discontinued the study due to a TEAE

Table 3. Treatment-Emergent Adverse Events (AC Subgroup, Safety Population)

Preferred Term, n (%)	APF530 Arm N = 293		Ondansetron Arm N = 303	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
TEAEs excluding injection-site reactions occurring in ≥ 10% of patients				
Fatigue	72 (24.6)	0	88 (29.0)	2 (0.7)
Constipation	72 (24.6)	0	54 (17.8)	0
Nausea	55 (18.8)	2 (0.7)	55 (18.2)	2 (0.7)
Headache	47 (16.0)	3 (1.0)	64 (21.1)	0
Injection-site reactions occurring in ≥ 5% of patients*				
Bruising	143 (48.8)	11 (3.8)	113 (37.3)	18 (5.9)
Pain	96 (32.8)	3 (1.0)	108 (35.6)	3 (1.0)
Erythema	57 (19.5)	2 (0.7)	87 (28.7)	1 (0.3)
Nodule	55 (18.8)	1 (0.3)	28 (9.2)	2 (0.7)
Swelling	30 (10.2)	2 (0.7)	35 (11.6)	0
Bleeding	20 (6.8)	0	29 (9.6)	1 (0.3)

*Both treatment arms received the tri(ethylene glycol) poly(orthoester) polymer subcutaneously.
TEAE = treatment-emergent adverse event.

Injection-Site Reactions

- The most frequently reported TEAEs were ISRs, occurring in 66.9% of patients in the APF530 arm and 60.7% in the ondansetron arm; all ISRs were conservatively considered treatment related (**Table 3**)
  - ISRs were generally mild or moderate and resolved by the end of the study
  - Severity of most ISRs was based on prespecified criteria of size and appearance only, rather than functional impairment

CONCLUSIONS

- APF530 is the first and only 5-HT_3 receptor antagonist to demonstrate superiority over another as part of the guideline-recommended regimen in a 3-drug versus 3-drug phase 3 efficacy trial
- In patients receiving AC-based HEC, numerical trends favored APF530 over ondansetron in CR in delayed-phase CINV, although statistical significance was not reached
- These findings suggest concordance with the significantly superior control of delayed-phase CINV observed with APF530 versus ondansetron in the overall study population
- Prevention of CINV in patients receiving AC-based HEC continues to be a challenge; these promising preliminary findings suggest a benefit of APF530 in this population and warrant further investigation

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Acknowledgments

Research support was provided by Heron Therapeutics, Inc. (formerly A.P. Pharma, Inc.). The authors wish to thank SciStrategy Communications for editorial and creative assistance in the preparation of this poster.