Poster 93

Phase 3 Trial of APF530 Versus Ondansetron, Each With a Neurokinin 1 Antagonist and Corticosteroid, for Prevention of Chemotherapy-Induced Nausea and Vomiting in Highly Emetogenic Chemotherapy Regimens (MAGIC Trial): Outcomes in Cisplatin-Based Regimens

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BACKGROUND

- Chemotherapy-induced nausea and vomiting (CINV) associated with highly emetogenic chemotherapy (HEC) is one of the most dreaded side effects of chemotherapy, adversely affecting patient quality of life and chemotherapy compliance[1]
- Cisplatin-based regimens, often used in women with gynecologic cancers, are classified as HEC[2]
- Women are at increased risk for CINV, which is especially difficult to manage in the delayed phase (24-120 h after chemotherapy)[3]
- Current antiemetic guidelines for HEC recommend a 3-drug regimen, comprising a 5-hydroxytryptamine 3 receptor antagonist (5-HT_3 RA), neurokinin 1 receptor antagonist (NK-1 RA), and corticosteroid (dexamethasone)[2,4-5]

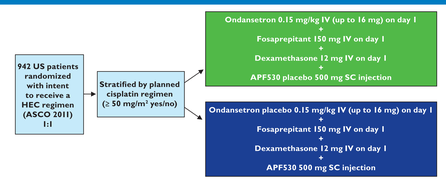
APF530 (Granisetron Injection, Extended Release)

- APF530 is a new formulation of 2% granisetron and a viscous bioerodible Biochronomer® tri(ethylene glycol) poly(orthoester) vehicle that undergoes controlled hydrolysis to provide extended release of granisetron for the prevention of both acute (0-24 h after chemotherapy) and delayed CINV[6]
- A single subcutaneous (SC) dose of APF530 provides therapeutic concentrations of granisetron for ≥ 5 days[7]
- In the phase 3 MAGIC trial, APF530 demonstrated superior complete response (CR; no emesis and no rescue medication use) in delayed CINV with HEC versus ondansetron (64.7% vs 56.6%; $P = 0.014$; 8% absolute improvement), each with an NK-1 RA and dexamethasone (NCT02106494)[8]
- This subgroup analysis evaluated the efficacy and safety of an APF530 regimen in patients receiving a cisplatin-based HEC regimen

METHODS

- MAGIC was a prospective, randomized, double-blind, double-dummy, multicenter phase 3 trial (**Figure 1**)
- 942 patients in the United States were enrolled, all with histologically or cytologically confirmed malignancy and scheduled to receive single-day HEC (ASCO 2011 emetogenicity criteria)
- Cancer type for each patient was not captured
- Patients were stratified by planned cisplatin ≥ 50 mg/m^2 (yes/no) and randomized 1:1 to APF530 500 mg SC (granisetron 10 mg) or ondansetron 0.15 mg/kg intravenously (IV)
- Patients were scheduled to receive concomitant dexamethasone 12 mg IV and fosaprepitant 150 mg IV on day 1 and oral dexamethasone 8 mg once on day 2 and 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
- The 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 difference using a modified intent-to-treat population (mITT; 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 (received study drug)
  - TEAEs with a possible, probable, or definite relationship to study treatment, as determined by the investigator, were considered treatment related

Exploratory Analysis of the Cisplatin Subgroup

- An exploratory analysis of efficacy and safety was conducted using the subgroup of patients who received a cisplatin-containing HEC regimen (≥ 50 mg/m^2)
- This analysis was not powered to detect treatment differences

RESULTS

Patients

- Among the 902 patients in the MAGIC trial mITT population (APF530 arm, 450; ondansetron arm, 452), 251 (28%) received cisplatin-based HEC regimens (APF530 arm, 125; ondansetron arm, 126)
- Baseline demographics were similar between treatment arms (**Table 1**)
  - The proportion of female patients was 40.8% in the APF530 arm and 48.4% in the ondansetron arm

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

	APF530 Arm N = 125	Ondansetron Arm N = 126
Age, mean (SD), y	61.6 (9.5)	61.4 (10.6)
Female, n (%)	51 (40.8)	61 (48.4)
Ethnicity, n (%) Not Hispanic/Latino Hispanic/Latino/other	 116 (92.8) 9 (7.2)	 116 (92.1) 10 (7.9)
Race, white, n (%)	102 (81.6)	115 (91.3)
Body mass index (kg/m^2) n Mean (SD)	 119 28.0 (6.5)	 122 28.1 (6.8)
ECOG PS, n (%) 0 1 Unknown	 72 (57.6) 51 (40.8) 2 (1.6)	 75 (59.5) 51 (40.5) 0
Currently drink alcohol, n (%) Any ≥ 8 drinks/wk	 47 (37.6) 8 (6.4)	 46 (36.5) 8 (6.3)
Currently smoke tobacco, n (%)	27 (21.6)	34 (27.0)

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

- The most common chemotherapy regimen was cisplatin + gemcitabine in 27.1% of patients in the cisplatin subgroup (APF530 arm, 24.8%; ondansetron arm, 29.4%)

Efficacy

- In the cisplatin subgroup, delayed-phase CR was numerically higher in the APF530 arm versus the ondansetron arm, equating to an 8.5% treatment difference (**Table 2**)
  - Although this confidence interval contains 0, the result is consistent with the APF530 benefit in the overall population (8.0% treatment difference, 95% CI 1.7, 14.4; $P = 0.014$)[8]
- Similar trends favoring APF530 were found across overall and acute-phase CR and across all phases for CC and TR

Table 2. Complete Response, Complete Control, and Total Response (Cisplatin Subgroup, mITT Population)

Response and Phase, n (%)	APF530 Arm N = 125	Ondansetron Arm N = 126	Treatment Difference (95% CI), % (APF530 – Ondansetron)
Complete response Delayed Overall Acute	 81 (64.8) 76 (60.8) 105 (84.0)	 71 (56.3) 69 (54.8) 101 (80.2)	 8.5 (-3.6, 20.5) 6.0 (-6.2, 18.2) 3.8 (-5.6, 13.3)
Complete control Delayed Overall Acute	 77 (61.6) 73 (58.4) 105 (84.0)	 67 (53.2) 64 (50.8) 96 (76.2)	 8.4 (-3.8, 20.6) 7.6 (-4.7, 19.9) 7.8 (-2.0, 17.6)
Total response Delayed Overall Acute	 60 (48.0) 60 (48.0) 102 (81.6)	 57 (45.2) 56 (44.4) 93 (73.8)	 2.8 (-9.6, 15.1) 3.6 (-8.8, 15.9) 7.8 (-2.5, 18.0)

CI = confidence interval; mITT = modified intent-to-treat.

- Among female patients in the cisplatin subgroup, CR, CC, and TR rates were numerically higher in the APF530 versus the ondansetron arm across all phases (**Table 3**)

Table 3. Complete Response, Complete Control, and Total Response Among Female Patients (Cisplatin Subgroup, mITT Population)

Response and Phase, n (%)	APF530 Arm N = 51	Ondansetron Arm N = 61	Treatment Difference (95% CI), % (APF530 – Ondansetron)
Complete response Delayed Overall Acute	 32 (62.7) 31 (60.8) 43 (84.3)	 32 (52.5) 31 (50.8) 46 (75.4)	 10.3 (-8.0, 28.5) 10.0 (-8.4, 28.3) 8.9 (-5.8, 23.6)
Complete control Delayed Overall Acute	 30 (58.8) 29 (56.9) 43 (84.3)	 31 (50.8) 30 (49.2) 44 (72.1)	 8.0 (-10.4, 26.4) 7.7 (-10.8, 26.2) 12.2 (-2.9, 27.2)
Total response Delayed Overall Acute	 27 (52.9) 27 (52.9) 42 (82.4)	 25 (41.0) 25 (41.0) 44 (72.1)	 12.0 (-6.5, 30.4) 12.0 (-6.5, 30.4) 10.2 (-5.1, 25.6)

CI = confidence interval; mITT = modified intent-to-treat.

Safety

- Consistent with the overall study population, APF530 was generally well tolerated in the cisplatin subgroup; no new safety signals were identified (**Table 4**)
- Most patients experienced ≥ 1 TEAE (APF530 arm, 72.2%; ondansetron arm, 66.4%)
- Excluding ISRs, the most common TEAEs were constipation, fatigue, nausea, diarrhea, dehydration, and headache
  - The most common treatment-related TEAEs in the APF530 and ondansetron arms were constipation (3.2% and 2.3%, respectively) and headache (3.2% and 4.7%, respectively)

Table 4. Treatment-Emergent Adverse Events (Cisplatin Subgroup, Safety Population)

Preferred Term, n (%)	APF530 Arm N = 126		Ondansetron Arm N = 128	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
TEAEs excluding injection-site reactions occurring in ≥ 10% of patients				
Constipation	24 (19.0)	1 (0.8)	9 (7.0)	0
Fatigue	22 (17.5)	2 (1.6)	18 (14.1)	1 (0.8)
Nausea	19 (15.1)	1 (0.8)	17 (13.3)	2 (1.6)
Diarrhea	19 (15.1)	1 (0.8)	15 (11.7)	0
Dehydration	14 (11.1)	5 (4.0)	4 (3.1)	0
Headache	7 (5.6)	0	15 (11.7)	0
Injection-site reactions occurring in ≥ 5% of patients*				
Bruising	35 (27.8)	7 (5.6)	31 (24.2)	6 (4.7)
Pain	33 (26.2)	0	41 (32.0)	4 (3.1)
Nodule	19 (15.1)	1 (0.8)	13 (10.2)	0
Erythema	14 (11.1)	0	32 (25.0)	0
Swelling	14 (11.1)	0	14 (10.9)	0

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

- The proportion of female cisplatin patients with ≥ 1 TEAE (APF530 arm, 76.9%; ondansetron arm, 64.5%) was similar to the overall cisplatin subgroup; most TEAEs were mild or moderate in severity

Injection-Site Reactions

- ISRs were the most frequently reported TEAEs, occurring in 49.2% and 54.7% of patients in the APF530 and ondansetron arms, respectively
  - For female cisplatin patients, ISRs were reported in 38.5% and 53.2% of those in the APF530 and ondansetron arms, respectively
- All ISRs were conservatively considered treatment related
- ISRs were generally mild or moderate in severity, and none led to study discontinuation
- No ISRs were considered serious TEAEs
- Severity of most ISRs was based on prespecified criteria of size and appearance, rather than functional impairment

CONCLUSIONS

- In this post hoc analysis of the cisplatin subgroup, consistent with the overall study, APF530 showed clinical benefit in delayed-phase CR in patients receiving cisplatin-based HEC, a particularly difficult to manage regimen commonly used for gynecologic cancers
- APF530 is the only 5-HT_3 RA to demonstrate superiority over another as part of the guideline-recommended regimen in a 3-drug versus 3-drug phase 3 efficacy trial

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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.