Abstract 68

Phase 3 Study of APF530 Versus Ondansetron With a Neurokinin 1 Antagonist + Corticosteroid in Preventing Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting: MAGIC Trial

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BACKGROUND

- Chemotherapeutic agents are classified by their emetogenicity, with the risk of chemotherapy-induced nausea and vomiting (CINV) being 31% to 90% with moderately emetogenic chemotherapy (MEC) and > 90% with highly emetogenic chemotherapy (HEC)[1]
- Most patients with breast cancer and receiving chemotherapy have MEC or HEC.[2] Importantly, anthracycline-based chemotherapy, commonly used in breast cancer, was recently reclassified by the American Society of Clinical Oncology (ASCO) from MEC to HEC[3]
- Current antiemetic treatment guidelines recommend a 3-drug regimen for patients receiving HEC, comprising a 5-hydroxyptamine 3 receptor antagonist (5-HT_3 RA), neurokinin 1 receptor antagonist (NK-1 RA), and dexamethasone[2,3]
- In patients receiving HEC, no trial has demonstrated superiority of a 5-HT_3 RA over another when given as part of a 3-drug regimen with an NK-1 RA and dexamethasone
- Managing delayed (> 24-120 h) CINV associated with HEC is an unmet medical need

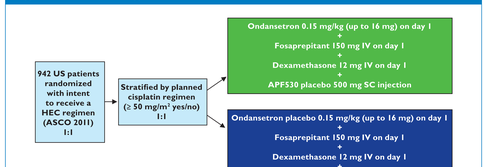
APF530 (Granisetron Injection, Extended-Release)

- APF530 is a novel formulation of 2% granisetron and a bioerodible tri(ethylene glycol) poly(orthoester) polymer designed to provide slow, sustained release of granisetron for prevention of both acute (0-24 h after chemotherapy) and delayed CINV[4]
- In a large, randomized, double-blind, phase 3 trial, APF530 was noninferior to palonosetron in preventing acute and delayed CINV in patients receiving MEC, and acute CINV in patients receiving HEC[4]
- The MAGIC Trial compared the efficacy and safety of APF530 in preventing CINV following HEC in a 3-drug regimen versus a standard 3-drug regimen with ondansetron

METHODS

- This prospective, randomized, double-blind, double-dummy, multicenter phase 3 trial
  - Enrolled 942 patients 18 to 80 years of age in the United States with histologically or cytologically confirmed malignancy and scheduled to receive single-day HEC (defined by ASCO 2011 emetogenicity criteria)
- Patients were stratified by planned cisplatin regimen (≥ 50 mg/m^2) and randomized 1:1 to either APF530 or ondansetron regimens (**Figure 1**)

Figure 1. Study Design



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

- Patients were scheduled to receive concomitant dexamethasone 8 mg PO once daily on day 2, and bid on days 3 and 4
- Rescue medication use was allowed at the physician's discretion
- The modified intent-to-treat (mITT) population (received HEC and study drug, and had postbaseline efficacy data) was used for efficacy analyses
- **Primary end point**
  Delayed-phase complete response (CR: no emetic episodes [vomit or retch], no rescue medication use)
- **Secondary end points**
  Overall-phase CR and rate of no emetic episodes, and overall- and delayed-phase complete control (CC: CR and no more than mild nausea)
- **Other exploratory end points**
  Presented for delayed and overall phases, including time to treatment failure (defined as emesis [vomit or retch] or rescue medication use), time to first nausea episode, rates of no nausea, rescue medication use, and patient-reported satisfaction with antiemetic therapy
- A post hoc analysis of nausea frequency was conducted
- The safety population (received study drug) was used for safety assessments
- Safety evaluations included treatment-emergent adverse event (TEAE) reporting by type and severity. TEAEs were adverse events that began within 8 days after study drug administration
  - All injection-site reactions (ISRs) were considered treatment emergent, regardless of the number of days following study drug administration
- This study was designed with 90% statistical power for the primary end point comparison
- Qualitative variables were analyzed using a Cochran-Mantel-Haenszel chi-square test controlled by planned use of cisplatin-based regimens ≥ 50 mg/m^2
  - To control for type I error, the significance level of tests for the 4 secondary end points was adjusted using the Hochberg method[5]

RESULTS

- A total of 902 patients were included in the mITT population
- Patient demographics and clinical characteristics were well balanced between treatment arms (**Table 1**)
  - The majority of patients were women, and most had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0

Table 1. Patient Demographics and Baseline Clinical Characteristics

	APF530 N = 450	Ondansetron N = 452
Age, mean (SD), y	55.7 (11.75)	55.6 (11.94)
Female, n (%)	358 (79.6)	373 (82.5)
Ethnicity, n (%) Not Hispanic/Latino Hispanic/Latino Other	 377 (83.8) 72 (16.0) 1 (0.2)	 384 (85.0) 68 (15.0) 0 (0)
Race, white, n (%)	368 (81.8)	372 (82.3)
Body mass index (kg/m^2) n mean (SD)	 436 29.72 (6.917)	 440 29.55 (6.872)
Planned cisplatin-based chemotherapy regimen ≥ 50 mg/m^2, n (%) Yes No	 124 (27.6) 326 (72.4)	 128 (28.3) 324 (71.7)
ECOG PS, n (%) 0 1 Unknown	 342 (76.0) 105 (23.3) 3 (0.7)	 336 (74.3) 114 (25.2) 2 (0.4)
Currently drink alcohol, n (%) Any ≥ 8 drinks/wk	 170 (37.8) 19 (4.2)	 167 (36.9) 15 (3.3)
Currently smoke tobacco, n (%)	70 (15.6)	72 (15.9)

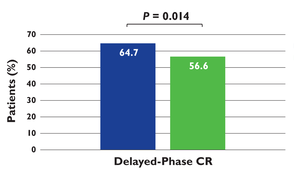
ECOG PS = Eastern Cooperative Oncology Group performance status; SD = standard deviation.

- The most common chemotherapy regimens received in both arms were
  - Anthracycline and cyclophosphamide based (64.6% APF530, 65.9% ondansetron)
  - Cisplatin based (27.7% APF530, 27.8% ondansetron)

Primary Efficacy End Point

- The APF530 regimen was associated with significantly greater delayed-phase CR, compared with the ondansetron regimen ($P = 0.014$; **Figure 2**),
  - Resulting in an absolute treatment difference of 8.0% (95% CI; 1.7, 14.4)
  - Equating to a relative 14.2% improvement in CR rate

Figure 2. Delayed-Phase Complete Response Rates



CR = complete response.

- Within the cisplatin stratum
  - Delayed-phase CR rates were 65.3% in the APF530 arm and 54.7% in the ondansetron arm,
    - Resulting in an absolute treatment difference of 10.6% (95% CI; -1.4, 22.7)
    - Equating to a relative 19.4% improvement in CR rate
- Within the non-cisplatin stratum
  - Delayed-phase CR rates were 64.4% in the APF530 arm and 57.4% in the ondansetron arm,
    - Resulting in an absolute treatment difference of 7.0% (95% CI; -0.5, 14.5)
    - Equating to a relative 12.2% improvement in CR rate

Secondary Efficacy End Points

- For each of the 4 secondary end points, the APF530 regimen showed numeric superiority, compared with the ondansetron regimen (**Table 2**)
- When adjusted for type I error, none reached statistical significance; however, APF530 was associated with a nearly significant increase in delayed-phase CC (unadjusted $P = 0.022$)

Table 2. Secondary Efficacy End Points

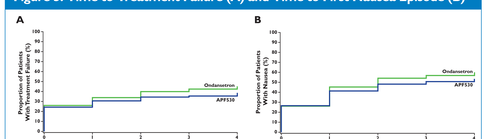
Parameter	APF530 N = 450 n (%)	Ondansetron N = 452 n (%)	Treatment Difference and Hochberg-Adjusted 95% CI (APF530 – Ondansetron)	Unadjusted *P* Value*	Hochberg Adjusted *P* Value†
Delayed-phase CC rate	273 (60.7)	240 (53.1)	7.6 (-0.6, 15.8)	0.022	0.088
Overall-phase CR rate	263 (58.4)	239 (52.9)	5.6 (-2.3, 13.5)	0.092	0.275
Overall-phase CC rate	246 (54.7)	224 (49.6)	5.1 (-2.3, 12.6)	0.123	0.247
Overall rate of no emesis	370 (82.2)	358 (79.2)	3.0 (-2.1, 8.1)	0.254	0.254

*P values based on the Cochran-Mantel-Haenszel chi-square test controlled by use of cisplatin-based regimens ≥ 50 mg/m^2 (yes/no).
†Significance level of the 4 tests adjusted using the method of Hochberg[5] to control overall type I error.
CC = complete control; CR = complete response.

Exploratory Efficacy End Points

- Time to treatment failure and time to first nausea episode are summarized in **Figure 3 A and B**
  - The proportion of patients with treatment failure was consistently higher across the study period with the ondansetron versus the APF530 regimen, although not statistically significantly ($P = 0.095$)
  - The proportion of patients who experienced a nausea episode was generally higher across the study period with the ondansetron versus the APF530 regimen

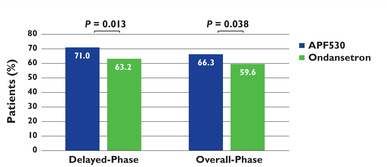
Figure 3. Time to Treatment Failure (A) and Time to First Nausea Episode (B)



*Days elapsed since study drug administration, where 0 = event or censored on study day 1 through 4 = event or censored on study day 5.

- Rates of no nausea were numerically higher with the APF530 versus the ondansetron regimen in the delayed (49.7% APF530, 44.2% ondansetron; $P = 0.099$) and overall phases (45.3% APF530, 44.2% ondansetron; $P = 0.138$); no statistically significant differences were found
- A post hoc analysis indicated that APF530 versus ondansetron was associated with less frequent nausea (0-2 vs ≥ 3 episodes) in the delayed ($P = 0.032$) and overall phases ($P = 0.048$)
- A significantly greater proportion of patients receiving the APF530 versus ondansetron regimen reported no rescue medication use in the delayed and overall phases (**Figure 4**)

Figure 4. Patients With No Rescue Medication Use



- Time to first use of rescue medication was significantly longer with APF530 versus ondansetron ($P = 0.049$)
- Patient-reported satisfaction with antiemetic therapy was higher with the APF530 versus ondansetron regimen in the delayed phase ($P = 0.040$)

Safety

- The APF530 regimen was generally well tolerated, with no new safety signals identified
- Most common TEAEs were ISRs, which were mostly mild or moderate in severity (**Table 3**)
  - A similar proportion of APF530 and ondansetron patients experienced ISRs

Table 3. Treatment-Emergent Adverse Events in ≥ 5% of Patients

	APF530 N = 456		Ondansetron N = 459	
Preferred Term, n (%)	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Patients with at least 1 event	413 (90.6)	89 (19.5)	411 (89.5)	89 (19.4)
Preferred term				
Neutropenia	26 (5.7)	17 (3.7)	30 (6.5)	24 (5.2)
Constipation	100 (21.9)	1 (0.2)	70 (15.3)	0 (0)
Nausea	76 (16.7)	3 (0.7)	74 (16.1)	4 (0.9)
Diarrhea	40 (8.8)	3 (0.7)	35 (7.6)	0 (0)
Dyspepsia	27 (5.9)	0 (0)	32 (7.0)	1 (0.2)
Fatigue	95 (20.8)	2 (0.4)	109 (23.7)	3 (0.7)
Decreased appetite	24 (5.3)	0 (0)	23 (5.0)	0 (0)
Dehydration	23 (5.0)	5 (1.1)	18 (3.9)	1 (0.2)
Headache	56 (12.3)	3 (0.7)	82 (17.9)	0 (0)
Dizziness	25 (5.5)	0 (0)	25 (5.4)	0 (0)
Insomnia	21 (4.6)	0 (0)	29 (6.3)	0 (0)
Injection-site reactions*				
Bruising	191 (41.9)	21 (4.6)	154 (33.6)	25 (5.4)
Pain	141 (30.9)	3 (0.7)	163 (35.5)	7 (1.5)
Nodule	82 (18.0)	2 (0.4)	45 (9.8)	2 (0.4)
Erythema	77 (16.9)	2 (0.4)	127 (27.7)	1 (0.2)
Swelling	45 (9.9)	2 (0.4)	53 (11.5)	0 (0)
Bleeding	23 (5.0)	0 (0)	36 (7.8)	1 (0.2)

*Both treatment groups received the tri(ethylene glycol) poly(orthoester) polymer SC.

- Most ISRs appeared within 1 to 3 days of injection, and resolved by study end
- Severity of most ISRs was based on prespecified criteria representing changes in size only, rather than functional impairment

CONCLUSIONS

- APF530, administered with fosaprepitant + dexamethasone, provided superior CR in delayed-phase CINV following HEC versus a standard 3-drug regimen of ondansetron with fosaprepitant + dexamethasone
- The APF530 regimen was associated with a clinical benefit over the ondansetron regimen in nausea control, rescue medication use, and patient satisfaction
- This was the first prospective, 3-drug versus 3-drug efficacy trial for the prevention of CINV

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