APF530: A Novel Extended-Release Formulation of Granisetron for 5-Day Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV)

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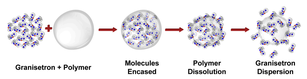
BACKGROUND

- Poorly controlled chemotherapy-induced nausea and vomiting (CINV) adversely affects patient health and quality of life[1,2]
- Chemotherapy agents are classified by their emetogenicity; highly emetogenic chemotherapy (HEC) is associated with a > 90% risk of CINV, and moderately emetogenic chemotherapy (MEC) with a 30% to 90% risk[3]
- CINV, particularly in the delayed phase (24-120 h) following HEC, remains a significant problem[4]

APF530: BIOCHRONOMER® TECHNOLOGY

- APF530 is a novel extended-release formulation of 2% granisetron and tri(ethylene glycol) poly(orthoester) (TEG-POE) polymer, known as Biochronomer[5] (**Figure 1**)
  - On injection into the subcutaneous (SC) tissue, the polymer undergoes degradation by controlled hydrolysis, resulting in slow, sustained release of granisetron for ≥ 5 days (> 120 h)[5,6]
  - One characteristic of Biochronomer technology is that the polymer remains in SC tissue while the drug is slowly released and the polymer degrades over time; this may lead to injection-site reactions (ISRs), including nodules, which eventually resolve

Figure 1. TEG-POE Polymer Allowing for Sustained Release of Granisetron



TEG-POE = tri(ethylene glycol) poly(orthoester).

- In a phase 3 trial (N = 1428), APF530 was noninferior to palonosetron in preventing acute (0-24 h) and delayed CINV after MEC and acute CINV after HEC[7,8]
- Nurses' understanding of APF530 administration, efficacy, and safety may improve CINV management

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Acknowledgments

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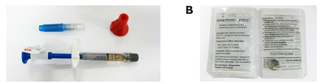
ADMINISTRATION AND HANDLING

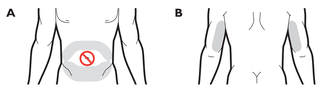
- APF530 is provided in a prefilled syringe with a special thin-wall 18-gauge needle and a warming pouch (**Figure 2**)

Figure 2. APF530 Syringe (A) and Warming Pouch (B)



- APF530 is administered by SC injection only
  - It cannot be administered intravenously, intraperitoneally, or intramuscularly
  - Injection may be given in the abdomen (**Figure 3A**) or upper arm (**Figure 3B**)

Figure 3. APF530 Administration to Abdomen (A) or Upper Arm (B)



- APF530 should be administered ≥ 30 minutes prior to chemotherapy
- APF530 is highly viscous and easier to inject when at body temperature
- APF530 should be stored refrigerated at ≤ 40°F and brought to body temperature before injection
  - APF530 can be put back in the refrigerator at any time, and rewarmed several times
  - APF530 can stay unrefrigerated for 7 days, and can be refrigerated up to 2 times
  - APF530 should not be frozen
- APF530 should be removed from refrigeration 30 to 60 minutes prior to use and allowed to reach room temperature (**Figure 4A**)
- The prefilled syringe must then be warmed using the warming pouch for 5 to 6 minutes to allow APF530 to reach body temperature (**Figure 4B**)
  - Convenient warming pouch enables easy administration of APF530
  - Warming bag will stay at the optimal temperature (104°F) for up to 15 minutes
  - If more time elapses, a second warming pouch may be used
- A topical anesthetic may be used prior to injection
- APF530 is injected with a slow, firm, and steady push and may take 20 to 30 seconds to deliver the entire dose (**Figure 4C**)
  - Application of greater pressure on the plunger does not expel APF530 faster

Figure 4. APF530 Warming and Administration Procedure

OBJECTIVES

- The phase 3 MAGIC trial compared APF530 versus ondansetron, each in a guideline-recommended 3-drug regimen of a 5-hydroxytryptamine 3 ($5HT_3$) receptor antagonist (RA), neurokinin 1 RA, and corticosteroid
- The primary end point was delayed-phase complete response (CR, no emesis [vomit or retch], no rescue medication use)

METHODS

- This prospective, randomized, double-blind, double-dummy phase 3 trial was conducted at multiple centers in the United States (NCT02106494)
  - The trial enrolled 942 adult patients with histologically or cytologically confirmed malignancy, scheduled to receive their first cycle of single-day HEC (ASCO 2011 criteria[9])
  - Patients were randomly assigned 1:1 to APF530 500 mg SC (granisetron 10 mg) and ondansetron placebo intravenously (IV) or ondansetron 0.15 mg/kg IV (≤ 16 mg) and APF530 placebo SC
  - All patients were scheduled to receive fosaprepitant 150 mg IV and dexamethasone (DEX) 12 mg orally (PO) on day 1, and DEX 8 mg PO qd on day 2 and bid on days 3 and 4
- Stratification was by planned use of cisplatin-based regimens ≥ 50 mg/m² (yes/no)
- Safety evaluations included treatment-emergent adverse events (TEAEs), reported by type and severity, serious TEAEs, and TEAEs causing study discontinuation
- Patients were instructed by clinic staff on recording ISRs in diaries provided to them
  - Patients with grade 3 or 4 ISRs returned to clinic for evaluation of ISR
- All ISRs were conservatively considered treatment related
- Severity of most ISRs was based on prespecified criteria of size and appearance only, rather than functional impairment

RESULTS

Patients

- The modified intent-to-treat population included 902 patients
- Patient demographics were generally balanced between treatment arms (**Table 1**)
- The majority of patients were female and had an Eastern Cooperative Oncology Group performance status of 0 (**Table 1**)

Table 1. Baseline Patient Demographics

	APF530 N = 450	Ondansetron N = 452
Age, mean (SD), y	56 (12)	56 (12)
Female, n (%)	358 (80)	373 (83)
Ethnicity, n (%)		
Not Hispanic/Latino	377 (84)	384 (85)
Hispanic/Latino	72 (16)	68 (15)
Other	1 (< 1)	0
Race, white, n (%)	368 (82)	372 (82)
Body mass index (kg/m²)		
n	436	440
mean (SD)	30 (7)	30 (7)
Cisplatin-based chemotherapy regimen ≥ 50 mg/m²		
Yes	124 (28)	128 (28)
No	326 (72)	324 (72)
ECOG PS		
0	342 (76)	336 (74)
1	105 (23)	114 (25)
Unknown	3 (1)	2 (< 1)
Currently drink alcohol, n (%)		
Any	170 (38)	167 (37)
≥ 8 drinks/week	19 (4)	15 (3)
Currently smoke tobacco, n (%)	70 (16)	72 (16)

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

Efficacy

- In the delayed phase, CR was achieved in 291 (65%) patients in the APF530 arm and 256 (57%) patients in the ondansetron arm (treatment difference 8%; relative difference 14%; $P = 0.014$) (**Figure 5**)

Figure 5. Delayed-Phase Complete Response (CR) Rates

Safety

- The safety population included 915 patients
- TEAEs occurred at a similar frequency in both treatment arms (**Table 2**)
- Excluding ISRs, the most common TEAE was constipation (22%) in the APF530 arm and fatigue (24%) in the ondansetron arm (**Table 2**)
- Serious TEAEs occurred in 28 (6%) patients in the APF530 arm and 16 (3%) patients in the ondansetron arm
- TEAEs led to death in 2 (< 1%) patients in the APF530 arm and 1 (< 1%) patient in the ondansetron arm; none were considered related to study drug
- TEAEs led to study discontinuation in 6 (1%) patients in the APF530 arm and 3 (1%) patients in the ondansetron arm

Table 2. Treatment-Emergent Adverse Events

	APF530 N = 456		Ondansetron N = 459	
Preferred Term, n (%)	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Patients with at least 1 event	413 (91)	89 (20)	411 (90)	89 (19)
Treatment-emergent adverse events in ≥ 15% of patients				
Constipation	100 (22)	1 (< 1)	70 (15)	0
Nausea	76 (17)	3 (1)	74 (16)	4 (1)
Fatigue	95 (21)	2 (< 1)	109 (24)	3 (1)
Headache	56 (12)	3 (1)	82 (18)	0
Injection-site reactions in ≥ 5% of patients				
Bruising	191 (42)	21 (5)	154 (34)	25 (5)
Pain	141 (31)	3 (1)	163 (36)	7 (2)
Nodule	82 (18)	2 (< 1)	45 (10)	2 (< 1)
Erythema	77 (17)	2 (< 1)	127 (28)	1 (< 1)
Swelling	45 (10)	2 (< 1)	53 (12)	0
Bleeding	23 (5)	0	36 (8)	1 (< 1)

- ISRs occurred at a similar frequency in both treatment arms (**Table 3**)
  - Patients in both arms received the Biochronomer SC injection as a constituent of APF530 or as a placebo injection (ondansetron arm)

Table 3. Overall Summary of ISRs

Preferred Term, n (%)	APF530 N = 456	Ondansetron N = 459
Patients with at least 1 treatment-related ISR	282 (62)	273 (59)
Patients with at least 1 serious ISR	1 (< 1)	0
Patients with at least 1 treatment-related serious ISR	1 (< 1)	0
Patients with at least 1 ISR with outcome of death	0	0
Patients with at least 1 ISR leading to study discontinuation	0	0
Patients with at least 1 ISR by severity		
Mild	177 (39)	166 (36)
Moderate	77 (17)	74 (16)
Severe	28 (6)	33 (7)

ISRs = injection-site reactions.

- No ISRs led to death or study discontinuation
- The majority of ISRs were mild or moderate (**Table 3**)
- The majority of ISRs appeared within 1 to 3 days of injection in both arms; among ISRs that appeared > 8 days after administration, injection-site nodules were the most common
- Most ISRs resolved by study end (APF530, 92%; ondansetron, 95%)
- Median ISR duration was the longest for injection-site nodules (APF530 arm, 4 days; ondansetron, 1 day)
  - Occurrence of nodules is consistent with extended-release Biochronomer formulation
- Patients receiving APF530 and concomitant medication affecting platelet function or coagulation were at greater risk of developing grade 3 injection-site bruising, bleeding, or hematoma
- White patients, compared with nonwhite patients, appeared to be at greater risk of developing injection-site bruising, bleeding, or hematoma, presumably due to ease of identifying bruising on lighter versus darker skin

CONCLUSIONS

- In this first US 3-drug versus 3-drug phase 3 efficacy trial for CINV prevention, APF530 versus ondansetron provided superior CR in the delayed phase following HEC
- The APF530 regimen was generally well tolerated
  - Majority of ISRs were mild to moderate and resolved by study end
  - There were no new or unexpected safety findings
- In our extensive experience, APF530 administration in the abdomen or upper arm was easy using the prefilled syringe and warming pouch
- These and previous studies indicate that APF530 SC may provide an effective and convenient treatment option for CINV control over the entire 5-day period following MEC or HEC

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