Poster 20

APF530: Pharmacokinetics and Efficacy of Extended-Release Granisetron Injection in the Prevention of Acute and Delayed Chemotherapy-Induced Nausea and Vomiting

Presented by ChauHwei Fu

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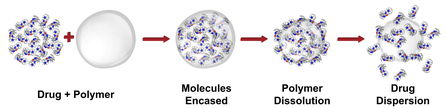
BACKGROUND

- Uncontrolled chemotherapy-induced nausea and vomiting (CINV) associated with moderately or highly emetogenic chemotherapy (MEC or HEC) may adversely affect quality of life and chemotherapy adherence[1,2]
- In particular, prevention of delayed CINV (>24-120 h after chemotherapy) remains a clinical challenge[2]
- Current antiemetic guidelines recommend a 5-hydroxytryptamine 3 (5-HT_3) receptor antagonist (RA) + corticosteroid for patients receiving MEC and a 3-drug combination (5-HT_3 RA + neurokinin 1 [NK-1] RA + corticosteroid) for patients receiving HEC[3-5]

APF530 (Granisetron Injection, Extended Release)

- APF530 is a novel, extended-release polymer formulation of the 5-HT_3 RA granisetron using new Biochronomer® technology[6]
- APF530 comprises 2% granisetron and a viscous bioerodible tri(ethylene glycol) poly(orthoester) vehicle that undergoes controlled hydrolysis to provide extended release for prevention of acute (0-24 h after chemotherapy) and delayed CINV (**Figure 1**)[6]

Figure 1. APF530: A Novel, Extended-Release Polymer Formulation of Granisetron Using Biochronomer® Technology



PHARMACOKINETICS OF APF530

Phase 2 Pharmacokinetic Studies

- Summary methods from phase 2 APF530 trials are shown in **Table 1**

Table 1. APF530 Phase 2 Trials

Trial Design	Population	Treatment	Objective
US sequential ascending-dose pharmacokinetic phase 2 trial	Patients with cancer scheduled to receive single-day MEC or HEC*	APF530 250, 500, or 750 mg SC (5, 10, or 15 mg granisetron) 30-60 min before chemotherapy	*Primary:* Determine the pharmacokinetic profile of APF530 from plasma granisetron measurements from predose to 168 h. Safety and efficacy were also evaluated
EU randomized pharmacokinetic phase 2 trial		APF530 250 or 500 mg SC 30-60 min before chemotherapy	

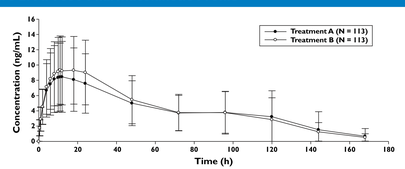
*Determined by Hesketh emetogenicity criteria.[7]
HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy.

- In these 2 phase 2 studies (N = 80), APF530 had dose-proportional pharmacokinetics and maintained therapeutic granisetron concentrations for at least 168 hours[8]
- Time to maximum plasma concentration (t_{max}) was ~24 hours (range, 19-32 h), and half-life ($t_{1/2}$) was 26 to 34 hours
- Median t_{max}, exposure, and $t_{1/2}$ were similar for APF530 250 and 500 mg in both trials, with no differences between MEC and HEC

Phase 1 Bioavailability Study

- A 2-sequence crossover bioavailability study compared APF530 500 mg SC administration in the upper left quadrant of the abdomen with that in the nondominant upper arm of healthy subjects
- Based on results from the phase 2 and 3 trials, the 500 mg APF530 dose was chosen for a bioavailability study
- APF530 SC abdominal and upper-arm routes of administration were bioequivalent (**Figure 2**); 90% CIs of geometric mean ratios were 106%-118% and 102%-110% for maximum concentration (C_{max}) and area under the curve from time zero to infinity ($AUC_{0\text{-}inf}$), respectively[9]

Figure 2. APF530 Pharmacokinetic Profile



Treatment A = upper left quadrant abdomen; Treatment B = nondominant upper arm.

EFFICACY OF APF530

- Summary methods from phase 3 APF530 trials are shown in **Table 2**

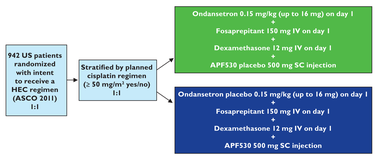
Table 2. APF530 Phase 3 Trials

Trial Design	Population	Treatment	Objective(s)
Randomized, double-blind, double-dummy, multicenter noninferiority trial	Patients with cancer scheduled to receive single-day MEC or HEC*	APF530 250 or 500 mg SC vs Palo 0.25 mg IV (each + Dex†)	*Primary:* Demonstrate noninferiority of APF530 to Palo for acute CINV after MEC or HEC, or delayed CINV after MEC, and superiority of APF530 to Palo for delayed CINV after HEC
Randomized, double-blind, double-dummy multicenter trial (MAGIC Trial)	Patients with cancer scheduled to receive single-day HEC‡	APF530 500 mg SC vs Ond 0.15 mg/kg (each + Dex† and Fos) (**Figure 3**)	*Primary:* Demonstrate superiority of APF530 to Ond for delayed CINV after HEC

*Hesketh emetogenicity criteria;[7] post hoc reanalysis done by ASCO 2011 criteria.[3]
†On day 1: 8 mg Dex IV for MEC, 20 mg Dex IV for HEC; on days 2-4: 8 mg Dex orally twice daily for HEC (noninferiority trial), 8 mg Dex orally once daily on day 2, twice daily on day 3-4 (MAGIC trial).
‡ASCO 2011 emetogenicity criteria.[3]
CINV = chemotherapy-induced nausea and vomiting; Dex = dexamethasone; Fos = fosaprepitant; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; Ond = ondansetron; Palo = palonosetron.

- For the phase 3 trials, the primary efficacy end point was complete response (CR; no emetic episodes and no rescue medication use) in the modified intent-to-treat population (mITT; all patients who received study drug and had postbaseline efficacy data)
- CR was assessed in acute, delayed, and overall (0-120 h) phases

Figure 3. Phase 3 MAGIC Trial Design



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

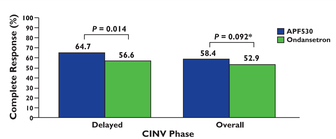
Noninferiority Trial (ASCO Reanalysis)

- In this trial (N = 1299), APF530 500 mg was noninferior to palonosetron (Palo) in preventing acute and delayed CINV after MEC and acute CINV after HEC[10,11]
- APF530 was not superior to Palo in preventing delayed CINV after HEC, but CR rates were numerically higher with APF530 500 mg (55.8%) versus Palo (50.5%)
- APF530 demonstrated sustained efficacy over multiple MEC or HEC cycles[12]

MAGIC Comparative Trial

- Baseline demographics were similar across treatment arms
  - Overall, mean age was 56 years, 81% of patients were female, and 75% had Eastern Cooperative Oncology Group performance status of 0
  - 28% received cisplatin-based HEC regimens, and 65% received anthracycline + cyclophosphamide-based regimens
- In the MAGIC trial (N = 902), the APF530 arm was superior to the ondansetron (Ond) arm in preventing delayed CINV after HEC[13]
- CR rate in the delayed phase (primary end point) was significantly higher in the APF530 arm (64.7%) than in the Ond arm (56.6%); *P* = 0.014 (**Figure 4**)

Figure 4. MAGIC Trial: Complete Response Rates in Delayed and Overall Phases of CINV in Patients Receiving HEC



*P values for secondary end points are unadjusted for multiple testing.
CINV = chemotherapy-induced nausea and vomiting; HEC = highly emetogenic chemotherapy.

- A post hoc analysis indicated that the APF530 regimen was associated with less frequent nausea (0-2 vs ≥ 3 episodes) than the Ond regimen in the delayed phase (*P* = 0.032)
  - More patients in the APF530 arm reported no rescue medication use (*P* = 0.013) than in the Ond arm

SAFETY OF APF530

- Safety assessments for all trials included adverse events (AEs) and injection-site reactions (ISRs) (safety population; all patients who received study drug)
  - Most common ISRs were bruising and pain; most appeared within 1 to 3 days of injection and resolved by study end
- In the pharmacokinetic studies, treatment-emergent AEs (TEAEs) were not dose related and were mainly mild to moderate
  - Treatment-related TEAEs were as expected for granisetron
  - ISRs were generally mild and occurred in ≤ 20% of patients

Noninferiority Trial (ASCO Reanalysis)

- APF530 was generally well tolerated; in cycle 1, ~68% of patients in each group had an AE; most were mild and not treatment related[10]
  - Excluding ISRs, most common AEs were constipation (13%-16% of patients in each group), fatigue (12%-14%), and diarrhea (9%-11%)
  - The most common treatment-related AEs were mild constipation (~3% in each group) and mild headache (1%-2%)
- ISRs occurred in all treatment groups, and at a higher frequency in APF530 versus Palo groups
  - The most frequent ISRs were bruising (9%-20%), erythema (4%-11%), and nodules (1%-11%)
  - Treatment-related ISRs were more frequent in APF530 versus Palo groups, but were typically mild and resolved over time; the most frequent treatment-related ISR was bruising (APF530, 13%-16%; Palo, 3%)

MAGIC Comparative Trial

- APF530 was generally well tolerated; ~90% of patients had ≥ 1 TEAE; most were mild to moderate (**Table 3**)[12]
  - Excluding ISRs, the most common TEAEs in APF530 and Ond arms were constipation, fatigue, nausea, and headache
  - The most common treatment-related TEAEs in APF530 and Ond arms, respectively, were constipation (6% vs 5%) and headache (6% vs 5%)
- ISRs occurred in 62% and 60% of APF530 and Ond arms, respectively; the most common were bruising and pain; most resolved by study end
  - ISR severity was primarily based on prespecified criteria of size and appearance, rather than functional impairment

Table 3. MAGIC Trial: Treatment-Emergent Adverse Events

	APF530 Arm N = 456		Ond Arm N = 459	
Preferred Term, n (%)	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
TEAEs (excluding injection-site reactions) in ≥ 10% of patients in any arm				
Constipation	100 (22)	1 (< 1)	70 (15)	0
Fatigue	95 (21)	2 (< 1)	109 (24)	3 (1)
Nausea	76 (17)	3 (1)	74 (16)	4 (1)
Headache	56 (12)	3 (1)	82 (18)	0
Injection-site reactions in ≥ 10% of patients in any arm*				
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)	1 (< 1)
Erythema	77 (17)	2 (< 1)	127 (28)	1 (< 1)

*Both treatment arms received the tri(ethylene glycol) poly(orthoester) polymer subcutaneously.
Ond = ondansetron; TEAEs = treatment-emergent adverse events.

CONCLUSIONS

- A single APF530 SC injection provides sustained therapeutic granisetron concentrations for ≥ 5 days
- APF530, as part of a guideline-recommended 3-drug regimen, demonstrated superiority versus Ond in preventing delayed CINV after HEC and was well tolerated
- Together with the earlier noninferiority trial, results suggest that a single SC injection of APF530 may be a convenient outpatient treatment option for preventing CINV after MEC or HEC

REFERENCES

1. Van Laar et al. *Support Care Cancer.* 2015;23:151-157.
2. Bloechl-Daum et al. *J Clin Oncol.* 2006;24:4472-4478.
3. Basch et al. *J Clin Oncol.* 2011;29:4189-4198.
4. NCCN Clinical Practice Guidelines in Oncology: Antiemesis—v2.2015.
5. Roila et al. *Ann Oncol.* 2010;21(suppl 5):v232-v243.
6. Ottoboni et al. *J Exp Pharmacol.* 2014;6:15-21.
7. Hesketh et al. *J Clin Oncol.* 1997;15:103-109.
8. Gabrail et al. *Cancer Manag Res.* 2015;7:83-92.
9. Morrison et al. MASCC 2015. Abstract 11-16-P.
10. Raftopoulos et al. *Support Care Cancer.* 2015;23:723-732.
11. Raftopoulos et al. *Future Oncol.* 2015;11:2541-2551.
12. Boccia et al. *J Community Support Oncol.* 2015;13:38-46.
13. Schnadig et al. *J Clin Oncol.* 2015;33 (suppl). Abstract 68.

Acknowledgments

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