Abstract 11-16-P

Phase 1 Bioavailability Study Comparing 2 Different Subcutaneous Routes of Administration for APF530

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BACKGROUND

- Chemotherapy-induced nausea and vomiting (CINV) is common in patients with cancer receiving chemotherapy and is often poorly controlled[1-3]
- An important risk factor for CINV is emetogenicity of the chemotherapy regimen; moderately (MEC) and highly (HEC) emetogenic chemotherapies are associated with the highest incidence of CINV[4]
- 5-Hydroxytryptamine type 3 (5-HT_3) antagonists (eg, granisetron) are first-line therapies for CINV prevention[1-3]
- APF530 is a novel formulation of 2% granisetron and a bioerodible tri(ethylene glycol) poly(orthoester) (TEG-POE) polymer designed to provide slow and sustained release of granisetron for the prevention of both acute (0-24 h) and delayed (24-120 h) CINV associated with MEC and HEC[5,6]
- In clinical studies of patients undergoing chemotherapy, a single dose of subcutaneously (SC) administered APF530 provided sustained therapeutic granisetron levels for over 5 days (> 120 h)[2]
- 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[6]
- Preliminary results from a phase 3 trial demonstrated that APF530 versus ondansetron, each given as a 3-drug regimen with fosaprepitant and dexamethasone, provided superior control of delayed-phase CINV associated with HEC (P=0.014)[7]
- It is important to understand the administration of APF530, how its viscosity relates to its duration of action, and why it is administered as a single SC injection

OBJECTIVES

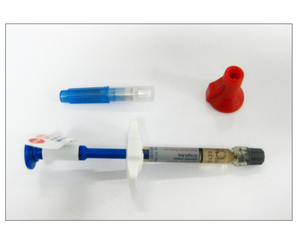
- The primary objective of this study was to compare the bioavailability of 2 different routes of administration of a single SC dose of APF530 500 mg
  - Administration routes: upper left quadrant (ULQ) of the abdomen, and nondominant upper arm
- The secondary objective was to assess the safety and tolerability of APF530 for each administration route

ADMINISTRATION AND HANDLING

- APF530 is provided in a prefilled syringe with a special thin-wall 18-gauge needle, with a sodium acetate syringe warmer (**Figure 1**)

Figure 1. APF530 Product Syringe (A) and Sodium Acetate Syringe Warmer (B)

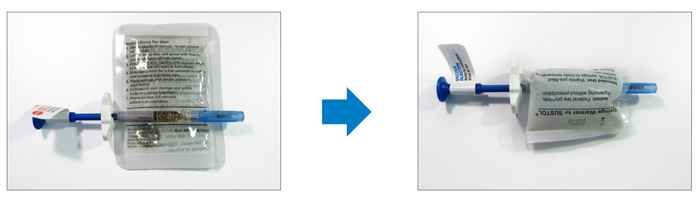
A



B

- The bioerodible polymer used in APF530 viscous, so the force required to inject it is directly proportional to the product's temperature
- APF530 should be warmed to body temperature prior to injection
- APF530 should be refrigerated (stored at 40°F or below), then removed 60 minutes prior to use and allowed to reach room temperature
- The prefilled syringe must then be warmed for at least 5 minutes; this will allow APF530 to reach body temperature (**Figure 2**)
  - The sodium acetate syringe warmer will stay at the optimal body temperature for up to 15 minutes
  - APF530 can be refrigerated and rewarmed
  - APF530 can stay unrefrigerated for 7 days
  - Once the product has been warmed and a topical anesthetic applied to the skin, APF530 is injected SC over 20 to 30 seconds

Figure 2. APF530 Warming Procedure

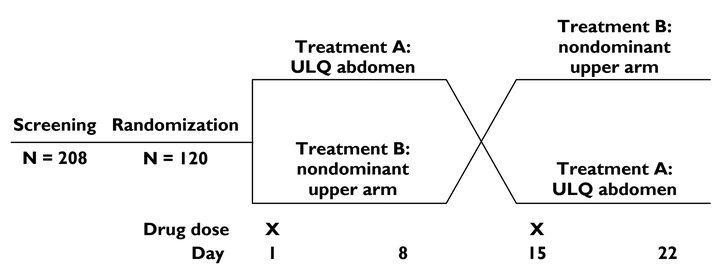


- Bioequivalence across different routes of administration is an important therapeutic consideration

METHODS

- In this phase 1, two-sequence crossover study (**Figure 3**)
  - Healthy male and female subjects were randomized to receive APF530 500 mg SC via the nondominant upper arm or ULQ of the abdomen on day 1
  - Subjects crossed over on day 15 to receive APF530 via the other route
- Plasma samples were obtained to assess granisetron pharmacokinetics by a noncompartmental model analysis
- Safety was assessed by evaluating adverse events (AEs), including injection-site reactions (ISRs), treatment-emergent AEs (TEAEs), serious AEs, and AEs causing study discontinuation; vital signs; physical examination; electrocardiogram (ECG); and clinical laboratory testing

Figure 3. Study Diagram



ULQ = upper left quadrant.

RESULTS

Subjects

- 111 of 120 randomized subjects completed the study
  - 116 received treatment A (ULQ abdomen), and 117 received treatment B (nondominant upper arm)
  - 9 discontinued from the study, none due to an AE
  - There were no deaths in this study
- Baseline demographics were generally similar among treatment groups (**Table 1**)

Table 1. Baseline Demographics

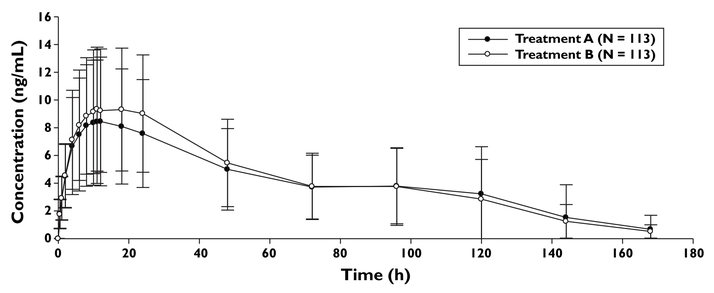
	Sequence AB n = 60	Sequence BA n = 60	Total N = 120
Age, median (range), y	31 (19-55)	30 (19-55)	31 (19-55)
Sex, n (%)			
Female	28 (47)	28 (47)	56 (47)
Male	32 (53)	32 (53)	64 (53)
Race, n (%)			
American Indian/Alaskan Native	1 (2)	1 (2)	2 (2)
Asian	0 (0)	1 (2)	1 (1)
Black/African American	9 (15)	4 (7)	13 (11)
White	50 (83)	54 (90)	104 (87)
Smoking status, n (%)			
Current tobacco user	1 (2)	7 (12)	8 (7)
Former tobacco user	21 (35)	14 (23)	35 (30)
Non–tobacco user	38 (63)	39 (65)	77 (64)
Body mass index, median (range), kg/m^2	28 (19-35)	30 (19-35)	28 (19-35)

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

Bioavailability

- 113 of 120 randomized subjects were included in the pharmacokinetic analysis
  - The 2 routes of administration were bioequivalent, providing ≥120 hours of granisetron exposure (**Figure 4**)

Figure 4. APF530 Pharmacokinetic Profile



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

- Least squares mean (LSM) ratio results confirmed bioequivalence between the 2 routes of administration (**Table 2**)
  - There was slightly more variation between the 2 routes in terms of granisetron absorption rate (maximum concentration [C_{max}]), with treatment B (nondominant upper arm) showing slightly higher peaks and more variability

Table 2. Statistical Comparisons of APF530 Pharmacokinetic Parameters

Parameter	LSM* Treatment A	LSM* Treatment B	LSM Ratio (%)	90% CI of the Ratio	Within-Subject % CV*
C_{max}	9	10	112	(106-118)	24
AUC_{0-t}	564	608	108	(104-112)	17
AUC_{0-inf}	584	619	106	(102-110)	16

*Within-subject % CV = 100 ×($\sqrt{e^{MSE}-1}$) where MSE is the mean square error from ANOVA.
Treatment A = upper left quadrant abdomen; treatment B = nondominant upper arm.
ANOVA = analysis of variance; AUC_{0-inf} = area under the concentration-time curve to infinity; AUC_{0-t} = area under the concentration-time curve to last measurable concentration; CI = confidence interval; C_{max} = maximum concentration; LSM = least squares mean.

Safety

- 91% of 116 subjects receiving abdominal injections (treatment A) and 77% of 117 subjects receiving arm injections (treatment B) experienced a treatment-related TEAE
- The majority of TEAEs were mild or moderate (**Table 3**)
  - Overall frequency of TEAEs was higher with treatment A, while severity was proportionally similar across treatment groups
  - Two subjects in treatment A experienced severe TEAEs of injection-site bruising/hematoma (defined per protocol as bruising > 4 cm), and were considered to be possibly related to study drug. All ISRs were conservatively assumed to be related to study drug administration

Table 3. Subjects With Treatment-Emergent Adverse Events

	Treatment A n = 116	Treatment B n = 117	Total N = 120
Severity, n (%)			
Mild	103 (89)	88 (75)	110 (92)
Moderate	23 (20)	9 (8)	29 (24)
Severe	2 (2)	0 (0)	2 (2)
Relationship to study drug, n (%)*			
Not related	6 (5)	6 (5)	12 (10)
Related†	106 (91)	90 (77)	113 (94)

*Relationship to study drug includes adverse events (AEs) recorded as possible, probable, or definite. AEs with missing causal relationship were recorded as possible.
†The majority of treatment-emergent AEs were mild or moderate injection-site reactions (ISRs); all ISRs were conservatively assumed to be related to study drug administration.
Treatment A = upper left quadrant abdomen; treatment B = nondominant upper arm.

- ISRs accounted for the majority of TEAEs and occurred in 89% of subjects (**Tables 4**)
  - ISRs occurred in 85% of subjects receiving abdominal injections (treatment A) and 69% of subjects receiving arm injections (treatment B)

Table 4. Treatment-Emergent Adverse Events Occurring in > 5% of Subjects

TEAE, n (%)	Treatment A N = 116	Treatment B N = 117	Total N = 120
Injection-site reactions			
Pain	74 (64)	70 (60)	90 (75)
Bruising/hematoma	44 (38)	39 (33)	63 (53)
Nodule	49 (42)	24 (21)	58 (48)
Erythema	29 (25)	11 (9)	37 (31)
Induration/swelling	9 (8)	12 (10)	18 (15)
Headache	26 (22)	25 (21)	43 (36)
Constipation	8 (7)	3 (3)	11 (9)
Nausea	5 (4)	4 (3)	9 (8)

Treatment A = upper left quadrant abdomen; treatment B = nondominant upper arm.
TEAE = treatment-emergent adverse event.

- The majority of ISRs were mild or moderate and no subjects discontinued the study due to ISR/TEAE
- The majority of ISRs (62%) had an onset of 1 to 3 days, while 28% had an onset of 4 to 8 days
- The mean maximum duration of an ISR ranged from 2 to 3 days, although the duration from onset to resolution may have been more than 7 days for 33% of subjects
- Physical examinations revealed no clinically significant findings, and no clinically important drug-related trends in laboratory values were identified
- No ECG-related TEAEs were reported
- No clinically relevant effects on acid-base balance were identified

CONCLUSIONS

- APF530 administration in the ULQ abdomen and the nondominant upper arm showed bioequivalence with no clinically relevant differences observed between treatment sites
  - The safety profile was similar to that of previous studies
  - This study indicates that different sites of administration for APF530 SC may be a potential option
- Single SC injections of APF530 may provide a convenient outpatient treatment option for preventing CINV following MEC or HEC

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