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Pharmacokinetics, safety, and efficacy of APF530 (extended-release granisetron) in patients receiving moderately or highly emetogenic chemotherapy: results of two Phase II trials

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Nashat Gabrail[1]
Ronald Yanagihara[2]
Marek Spaczyński[3]
William Cooper[4]
Erin O'Boyle[5]
Carrie Smith[1]
Ralph Boccia[6]

[1]Gabrail Cancer Center, Canton, OH, USA; [2]St Louise Regional Hospital, Gilroy, CA, USA; [3]Department of Gynecology, Obstetrics and Gynecologic Oncology, University of Medical Sciences, Poznan, Poland; [4]TFS International, Flemington, NJ, USA; [5]FibroGen, Inc., San Francisco, CA, USA; [6]Center for Cancer and Blood Disorders, Bethesda, MD, USA

Background: Despite advances with new therapies, a significant proportion of patients (>30%) suffer delayed-onset chemotherapy-induced nausea and vomiting (CINV) despite use of antiemetics. APF530 is a sustained-release subcutaneous (SC) formulation of granisetron for preventing CINV. APF530 pharmacokinetics, safety, and efficacy were studied in two open-label, single-dose Phase II trials (C2005-01 and C2007-01, respectively) in patients receiving moderately emetogenic chemotherapy or highly emetogenic chemotherapy.

Methods: In C2005-01, 45 patients received APF530 250, 500, or 750 mg SC (granisetron 5, 10, or 15 mg, respectively). In C2007-01, 35 patients were randomized to APF530 250 or 500 mg SC. Injections were given 30 to 60 minutes before single-day moderately emetogenic chemotherapy or highly emetogenic chemotherapy. Plasma granisetron was measured from predose to 168 hours after study drug administration. Safety and efficacy were also evaluated.

Results: APF530 pharmacokinetics were dose proportional, with slow absorption and elimination of granisetron after a single SC dose. Median time to maximum plasma concentration and half-life were similar for APF530 250 and 500 mg in both trials, with no differences between the groups receiving moderately and highly emetogenic chemotherapy. Exposure to granisetron was maintained at a therapeutic level over the delayed-onset phase, at least 168 hours. Adverse events in both trials were as expected for granisetron; injection site reactions (eg, erythema and induration) were predominantly mild and seen in ≤20% of patients. Complete responses (no emesis, with no rescue medication) were obtained in the acute, delayed, and overall phases in ≥80% and ≥75% of patients in both trials with the 250 and 500 mg doses, respectively.

Conclusion: After a single injection of APF530, there were dose-proportional pharmacokinetics and sustained concentrations of granisetron over 168 hours. The 250 and 500 mg doses were well tolerated and maintained therapeutic granisetron levels for ≥5 days.

Keywords: cancer, chemotherapy-induced nausea and vomiting, subcutaneous

Background

Control of cancer chemotherapy-induced nausea and vomiting (CINV) is paramount in maintaining patients' quality of life and their compliance with later chemotherapy.[1] Regimens may be classified as moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC), on the basis of the emetogenic potential of the individual agents.[2] Prevention of CINV is the goal; available antiemetics include serotonin (5-HT_3) receptor antagonists, neurokinin 1 (NK-1) receptor antagonists, and dexamethasone. Guidelines on the use of these agents in CINV management, based on the emetogenic potential of the chemotherapy regimen, have been published.[1,3,4]

Correspondence: Nashat Gabrail
Gabrail Cancer Center, 4875 Higbee Ave, NW, Canton, OH 44718, USA
Tel +1 330 492 3345
Fax +1 330 491 9763
Email ngabrailmd@aol.com

Delayed-onset CINV (occurring more than 24 hours after chemotherapy) is typically more difficult to control than acute-onset CINV (occurring 0–24 hours after chemotherapy),[1,3,4] and despite available antiemetics, CINV is undertreated, with more than 30% of patients continuing to experience CINV with current antiemetic treatments.[4,5]

APF530 is a subcutaneous (SC), sustained-release formulation of 2% granisetron in a polymer vehicle designed to provide a therapeutic level of the drug for ≥120 hours.[6] A double-blind, placebo-controlled, intrapatient dose-escalation Phase I study in healthy male subjects determined that single SC doses of APF530 are safe and well tolerated at 125, 250, 500, and 1,000 mg, with mild injection site reactions, no serious adverse events (AEs), and no clinically significant laboratory abnormalities or electrocardiographic (ECG) changes.[7,8]

The two previously unpublished Phase II studies presented here assessed the pharmacokinetic properties, safety, and efficacy of three doses of APF530, in patients receiving MEC or HEC.

Methods

Pharmacokinetics, safety, and efficacy of single SC injections of APF530 were assessed in two open-label multicenter Phase II trials in patients receiving MEC or HEC regimens. The first trial (C2005-01) was a sequential ascending dose study. The second study (C2007-01) was a randomized study with two doses of APF530.

Patients

Inclusion criteria were similar for the two Phase II studies. Eligible patients were at least 18 years old, males or nonpregnant females with cytologically or histologically confirmed cancer, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and scheduled to receive a single-day MEC or HEC regimen. C2005-01 was initially designed to enroll only patients with MEC; however, during the conduct of the trial, the decision was made to enroll patients receiving both MEC and HEC. Emetogenicity was defined according to Hesketh criteria.[2] Prior chemotherapy was allowed. In C2005-01, corticosteroids were permitted, although not required, in compliance with the current standard of care and were used in 84% of patients; in C2007-01, patients were required to be able to receive standard doses of dexamethasone as specified in the protocol.

Patients were not eligible if they received radiation therapy within 7 days prior to receiving APF530 or had scheduled radiation therapy or chemotherapy during the 14 (C2005-01) or 7 (C2007-01) days after receiving APF530. Use of CYP3A4 inhibitors was not permitted. In C2005-01, nausea of greater than mild severity or any vomiting within 24 hours prior to receiving APF530 was exclusionary. Patients with head and neck cancer or upper gastrointestinal cancer were not eligible.

In C2005-01, patients were not eligible if they received antiemetics or other prohibited medications within 10 days prior to receiving APF530. In C2007-01, patients were not eligible if they received granisetron, systemic corticosteroids, or other prohibited medications within 7 days prior to receiving APF530. Patients with a heart rate-corrected QT interval (QTc) interval >500 ms or a cardiac abnormality predisposing them to arrhythmia were also excluded.

The C2005-01 protocol was reviewed and approved by a central institutional review board, the Western Institutional Review Board. The C2007-01 protocol was reviewed and approved by an independent ethics committee for each investigational site. Both studies were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. C2007-01 was registered with European Union Drug Regulating Authorities Clinical Trials (EudraCT), as EudraCT number 2008-000469-53. C2005-01 was completed before requirements for trial registration.

Study design

C2005-01 patients were assigned to one of three ascending APF530 dose groups: 250 mg (containing granisetron 5 mg), 500 mg (containing granisetron 10 mg), and 750 mg (containing granisetron 15 mg). The decision to enroll in the next dose-escalation group was based on AEs and laboratory results with the lower dose. Doses were given by SC injection in the abdominal area 30 minutes before the start of chemotherapy. A local anesthetic, usually a lidocaine preparation or ethyl chloride spray, was applied to the area of the injection site prior to study drug administration. The study duration was 14 days. After a 7-day treatment and sample collection period, patients returned for a final follow-up visit 14±3 days after study drug administration. Patients were prescribed rescue medication (excluding granisetron) at the discretion of the investigator, to be used as needed in the event of vomiting.

In C2007-01, patients were randomly assigned to receive APF530 250 or 500 mg by SC injection 30 to 60 minutes before the scheduled chemotherapy. Dexamethasone 8 mg intravenously (IV) was given on day 0, in patients with MEC. Dexamethasone 20 mg IV was given on day 0, and 8 mg twice a day on days 1 to 3, in patients with HEC. The study

duration was 14±3 days. Patients were prescribed rescue medication as in the 2005-01 study.

Study objectives

The primary objective of both trials was to define the pharmacokinetic properties of granisetron after a single SC dose of APF530 in cancer patients receiving chemotherapy. Secondary objectives were to assess the safety of single SC injections of APF530 in patients receiving single-day MEC or HEC. Evaluation of efficacy in preventing acute-onset (0–24 hours) or delayed-onset (24–168 hours) CINV was an exploratory objective.

Assessments

Plasma granisetron concentrations were measured predose, prior to chemotherapy infusion (C2005-01), and at 2, 6, 24, 48, 72, 96, 120, 144, and 168 hours after APF530 administration. In C2007-01, additional time points were added at 4, 12, and 18 hours after APF530 administration. Measured pharmacokinetic parameters included area under the concentration–time curve (AUC) at 0 to 24 hours, AUC at 0 to 168 hours, maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), the elimination rate constant, and half-life ($t_{1/2}$) in both trials; and additionally, apparent total clearance, apparent volume of distribution, and mean residence time, in C2007-01.

Safety was assessed throughout the studies, based on vital signs, physical examination, clinical laboratory tests (only at screening in C2007-01), and 12-lead ECGs at screening (predose) and 168 hours (also at 48 hours in C2005-01), and included AEs, injection site reactions, and concomitant medications.

Efficacy was assessed by the number of emetic episodes, number of retching/dry heave episodes, nausea ratings, and rescue medication use during 7 days following the single dose of APF530, which were recorded in patient diaries and collected at each study visit (C2005-01). Alternatively, patients were interviewed at each visit, regarding the occurrence of nausea and emesis and use of rescue medication, with responses recorded (C2007-01).

Efficacy parameters included complete response (CR) (no emetic episodes and no use of rescue medication), complete control (CR with no more than mild nausea), and total response (CR with no nausea), and were summarized for the acute and delayed phases, for MEC and HEC.

Statistics

Noncompartmental methods and descriptive statistics were used to derive and analyze the pharmacokinetic parameters. Descriptive summaries were used for safety measurements by treatment group and preferred term. Efficacy was summarized by time interval and treatment group. Sample sizes were consistent with a previous pharmacokinetic study of palonosetron in patients with cancer receiving chemotherapy.[9]

Results

Patients

C2005-01 enrolled 45 male and female patients, and C2007-01 enrolled 35 female patients. Most patients had received prior chemotherapy (Table 1). Ovarian, breast, and lung cancers were most common (Table 2). Ovarian cancer affected 83% of women in C2007-01. More than half the patients received carboplatin-based chemotherapy, and 65% received an HEC regimen (Table 3).

Table 1 Patient demographics and baseline characteristics in both APF530 Phase II studies

Characteristic	C2005-01				C2007-01		
	APF530 250 mg n=17	APF530 500 mg n=15	APF530 750 mg n=13	APF530 Total n=45	APF530 250 mg n=17	APF530 500 mg n=18	APF530 Total n=35
Age, years, mean (SD)	67.4 (13.0)	59.9 (12.9)	64.3 (10.6)	64.0 (12.5)	55.8 (9.3)	55.5 (8.5)	55.7 (8.7)
Sex, female, %	41.2	73.3	69.2	60.0	100	100	100
Race, %							
Caucasian	64.7	66.7	84.6	71.1	100	100	100
Latino	23.5	13.3	7.7	15.6	0	0	0
Black	0	13.3	7.7	6.7	0	0	0
Other	11.8	6.7	0	6.7	0	0	0
ECOG PS, %							
0	47.1	33.3	38.5	40.0	64.7	66.7	65.7
1	52.9	66.7	61.5	60.0	35.3	27.8	31.4
2	0	0	0	0	0	5.6	2.9
Prior chemotherapy, %	88.2	73.3	61.5	77.8	52.9	66.7	60.0

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; SD, standard deviation.

Table 2 Current malignancies in patients in both APF530 Phase II studies

Current malignancy, %	APF530 250 mg n=34	APF530 500 mg n=33	APF530 750 mg n=13	APF530 Total n=80
Ovarian cancer	47.1	42.4	7.7	40.0
Breast cancer	11.8	15.2	38.5	17.0
Lung cancer	8.8	15.2*	38.5	16.3
Lymphoma/leukemia	17.7	3.0	0	8.8
Endometrial/ cervical/vulvar	8.8	15.2	0	8.8
Colorectal cancer	2.9	3.0	0	2.5
Bladder cancer	2.9	3.0*	0	2.5
Thymoma	0	3.0	7.7	2.5
Myeloma	0	3.0	7.7	2.5

Note: *One patient with both bladder cancer and lung cancer.

Patient dispositions and protocol deviations

C2005-01 patients receiving MEC (22 [49%]) or HEC (23 [51%]) were enrolled at six clinical sites in the United States; 17 received APF530 250 mg, 15 received APF530 500 mg, and 13 received APF530 750 mg. Three of 15 patients in the 500 mg group did not complete the study: two had unrelated serious AEs (one dysphagia; one dyspnea, malaise, and diaphoresis) and one withdrew consent (Table 4). After completing the study, one patient experienced fever and septic shock within 4 weeks after receiving APF530 and later died of underlying non-small-cell lung cancer (NSCLC).

Six patients scheduled to receive chemotherapy on days 1 and 8, or on days 1, 8, and 15 were allowed to enter the study by the medical monitors, and one also had head and neck cancer. All patients who received study drug were included in the safety analysis. Four patients who did not receive the full dose of study drug were excluded from the pharmacokinetic and efficacy analyses (N=41); five patients with missing samples were also excluded from the pharmacokinetic analysis (N=36).

C2007-01 patients were randomized at three sites in Poland; 17 received APF530 250 mg, and 18 received APF530 500 mg (Table 4). Data from six patients with minor deviations from the protocol were allowed by the medical monitor: five were >65 years of age, and one had enrolled in another trial within 30 days. Twelve patients missing up to three blood samples were included in the pharmacokinetic analysis. Two patients received restricted medications, one did not receive the full oral dose of dexamethasone on two occasions, and two did not have final ECGs available for analysis. These patients were included in the final analysis, and their inclusion did not confound the study results.

Table 3 Current chemotherapy for patients in both APF530 Phase II studies

Chemotherapy regimens and emetogenicity classification	APF530 250 mg n=34	APF530 500 mg n=33	APF530 750 mg n=13	APF530 Total n=80
Current chemotherapy, %				
Carboplatin and combinations	50.0	60.6	46.2	53.8
Cyclophosphamide-anthracycline	11.8	15.2	38.5	17.5
Cyclophosphamide and other combinations	5.9	3.0	7.7	5.0
Irinotecan, topotecan	8.8	12.1	0	8.8
Cisplatin combinations	11.8	6.1	0	7.5
Anthracyclines, other combinations	11.8	3.0	0	6.3
Gemcitabine-vinorelbine combination	0	0	7.7	1.3
Emetogenicity classification, %				
Hesketh 2	2.9	3.0	7.7	3.8
Hesketh 3 (MEC)	11.8	15.2	0	11.3
Hesketh 4 (MEC)	20.6	12.1	38.5	20.0
Hesketh 5 (HEC)	64.7	69.7	53.9	65.0

Abbreviations: HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy.

Pharmacokinetics

Both studies met their primary objective in defining the pharmacokinetic properties of granisetron after a single SC dose of APF530 (Tables 5 and 6). The rate (T_{max}) and extent of absorption (C_{max}) of granisetron from APF530 were generally dose proportional and consistent between the two studies. Granisetron was absorbed slowly – C_{max} occurred at approximately 24 hours (range, 19–32 hours), and the $t_{1/2}$ was 26 to 34 hours. No dose-related differences in the rate of absorption of granisetron from the APF530 polymer were apparent. Importantly, exposure to granisetron was maintained over the delayed-onset phase, for at least 168 hours (Figures 1 and 2). Mean plasma concentrations, in C2005-01, 168 hours after dosing were 0.579, 1.946, and 2.386 ng/mL for the 250, 500, and 750 mg dose groups, respectively.

In C2005-01, the comparison of $t_{1/2}$, T_{max}, and the elimination rate constant among the dose groups revealed no significant differences ($P \geq 0.309$, Kruskal–Wallis test), and regression analysis indicated dose proportionality for AUC and C_{max}. Large variability was seen within each dose group in both trials; the use of separate patient groups for each dose was likely to have contributed.

Table 4 Patient dispositions in both APF530 Phase II studies

Disposition	C2005-01				C2007-01		
	APF530 250 mg n=17	APF530 500 mg n=15	APF530 750 mg n=13	APF530 Total n=45	APF530 250 mg n=17	APF530 500 mg n=18	APF530 Total n=35
Completed study, %	100	80	100	93.3	100	88.9	94.3
Early withdrawal, %	0	20	0	6.7	0	11.1	5.7
Reason for early withdrawal, %							
Adverse events	0	13.3	0	4.4	0	0	0
Lack of efficacy	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Lost to follow up	0	0	0	0	0	0	0
Withdrawal of consent	0	0	0	0	0	0	0
Noncompliance	0	6.7	0	2.2	0	0	0
Investigator's decision	0	0	0	0	0	0	0
Incomplete blood sample collection	0	0	0	0	0	11.1	5.7

In C2005-01, various factors were assessed for their effect on the plasma profile of granisetron after APF530 administration. Minor differences were seen in the pharmacokinetic profile related to chemotherapy history (naïve vs previously exposed), emetogenic classification, alcohol or tobacco use, and anthracycline as a component of the chemotherapy. The greatest difference in mean AUC values was between smokers and nonsmokers, but with the large interindividual variability within each group, no meaningful differences in the plasma profiles could be attributed to any of these variables.

Table 5 Summary of granisetron pharmacokinetic parameters: study C2005-01

APF530 dose	Statistic	C_{max} ng/mL	T_{max}	AUC (ng·h/mL)		λz 1/h	$t_{1/2}$ h
				0–24	0–168		
250 mg	N	13	13	13	13	12	12
	Mean	11.60	24.61	188	740	0.024	33.78
	SD	6.83	14.88	93	722	0.011	14.72
	Min	4.48	6.00	72	141	0.01	14.45
	Median	10.80	23.13	170	590	0.022	31.69
	Max	31.80	47.98	432	3,008	0.05	64.58
500 mg	N	10	10	9	10	10	10
	Mean	17.81	28.73	256	1,385	0.033	26.16
	SD	12.90	13.86	144	1,348	0.016	12.85
	Min	4.43	6.00	86.9	285	0.01	10.95
	Median	12.25	24.46	217	764	0.028	25.38
	Max	40.50	49.42	520	4,291	0.06	52.55
750 mg	N	13	13	13	13	13	13
	Mean	29.76	26.15	423	2,148	0.024	33.62
	SD	17.47	10.32	257	1,207	0.010	12.01
	Min	5.95	6.00	100	435	0.01	14.16
	Median	28.00	24.00	403	1,954	0.023	29.69
	Max	77.70	47.55	1,189	4,370	0.05	49.21

Abbreviations: λz, elimination rate constant; AUC, area under the concentration–time curve; C_{max}, maximum plasma concentration; h, hours; max, maximum; min, minimum; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration.

Safety

Treatment-emergent AEs (TEAEs) in 82.2% of patients in C2005-01 and 51.4% of patients in C2007-01 did not generally appear to be dose related (Table 7). TEAEs were mostly mild to moderate and unrelated to the study drug.

In C2005-01, no clinically significant laboratory abnormalities were reported following APF530 administration. In C2007-01, clinically significant low red blood cell counts and low hemoglobin concentrations were reported in four patients. No clinically meaningful changes in vital signs, physical examinations, or ECGs were reported in either study.

AEs related to APF530 occurred in 28.9% of patients in C2005-01. In addition to injection site reactions, events related to APF530, and occurring in at least two patients, in C2005-01 were mild to moderate constipation (three patients) and mild to moderate headache (two patients). In C2007-01, the only related AEs, other than injection site reactions, were mild or moderate constipation in four patients (11.6%).

Injection site reactions in studies C2005-01 and C2007-01, respectively, included erythema (8.9% and 5.7%), induration (6.7% and 8.9%), bruising (4.4% and 5.7%), and tenderness or pain (2.2% and 2.9%). There were 19 reactions among 80 patients, 17 mild and two of moderate intensity.

Serious AEs in C2005-01 occurred in four patients: one patient died (related to the underlying disease); and among the remaining patients, one had dyspnea, malaise, and hyperhidrosis, one had intractable diarrhea, and one had dysphagia. All patients recovered. None of the events was related to the study drug. In C2007-01, serious AEs occurred in three patients: one had thrombocytopenia and anemia, one had anemia, and one had thrombocytopenia and abdominal pain. None of the serious AEs was considered related to the study drug, and there were no deaths during the study.

Table 6 Summary of granisetron pharmacokinetic parameters: study C2007-01

APF530 dose	Statistic	C_{max} ng/mL	T_{max} hours	AUC (ng·h/mL)		λz 1/h	$t_{1/2}$ hours	Cl/F mL/h	Vd/F mL	MRT hours
				0–24	0–168					
250 mg	N	17	17	17	15	12	12	12	12	12
	Mean	11.8	18.5	201	650	0.0239	31.6	8,496	367,608	51.7
	SD	11.6	7.5	195	358	0.0061	11.6	4,561	179,705	22.1
	Min	2.43	5.67	43.4	275	0.0108	22.3	3,498	123,043	24.3
	Median	9.17	22.8	145	521	0.0235	29.7	6,914	367,065	49.6
	Max	53.1	24.5	871	1,419	0.0311	64.2	17,532	697,100	96.6
	CV%	99	40	97	55	26	37	54	49	43
500 mg	N	18	18	18	17	10	10	10	10	10
	Mean	17.8	31.6	315	996	0.0270	28.8	27,499	943,758	48.3
	SD	23.6	27.5	458	1,025	0.0090	11.1	35,014	983,515	19.5
	Min	2.52	5.92	44.7	73.1	0.0133	17.2	2,675	71,855	28.9
	Median	10.1	22.9	147	571	0.0266	26.2	17,929	673,137	43.7
	Max	95.4	118	1,752	3,728	0.0403	52.3	120,649	3,425,926	91.8
	CV%	133	87	145	103	33	39	127	104	40

Abbreviations: λz, elimination rate constant; AUC, area under the concentration–time curve; C_{max}, maximum plasma concentration; Cl/F, apparent clearance; CV, coefficient of variation; h, hours; max, maximum; min, minimum; MRT, mean residence time; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration; Vd/F, apparent volume of distribution.

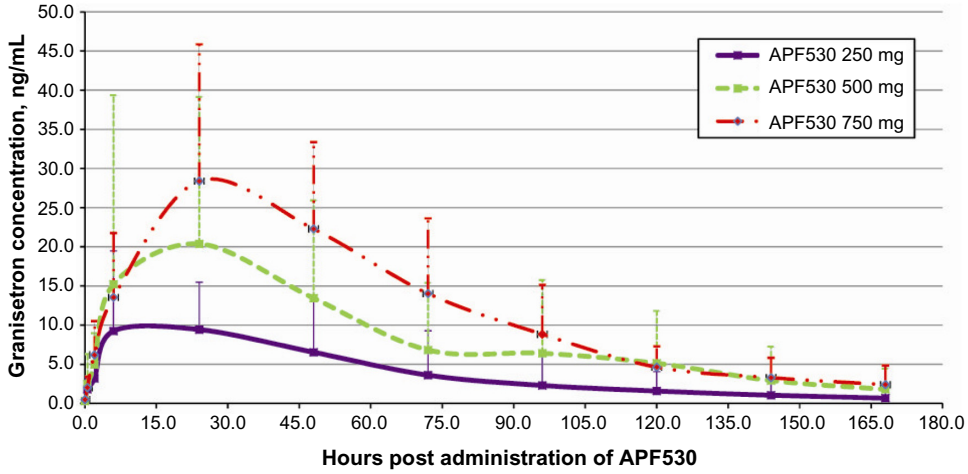

Figure 1 Mean (±SD) plasma granisetron concentration measured from 0 to 168 hours after APF530 administration. Granisetron concentrations are shown for APF530 250, 500, or 750 mg by SC injection (C2005-01).
Abbreviations: SC, subcutaneous; SD, standard deviation.

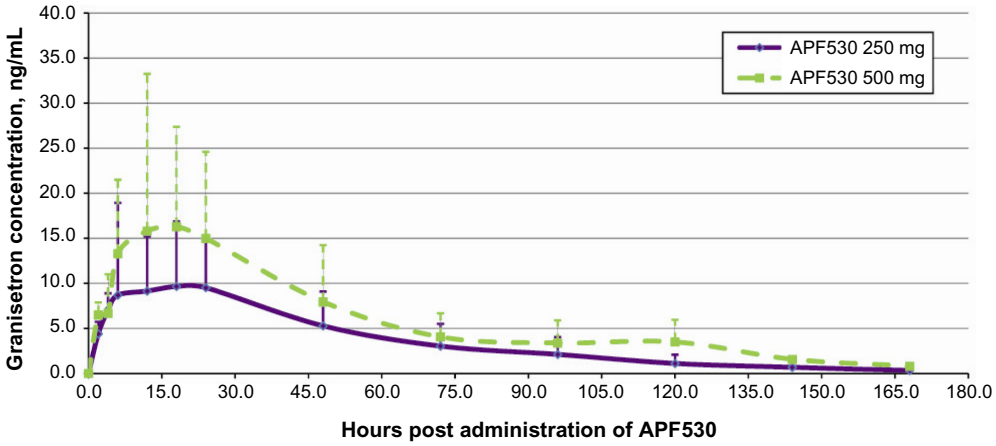

Figure 2 Mean (±SD) plasma granisetron concentration measured from 0 to 168 hours after administration. Granisetron concentrations are shown for APF530 250 or 500 mg by SC injection (C2007-01).
Abbreviations: SC, subcutaneous; SD, standard deviation.

Table 7 Treatment-emergent adverse events in both APF530 Phase II studies

Adverse event	C2005-01				C2007-01		
	APF530 250 mg n=17	APF530 500 mg n=15	APF530 750 mg n=13	APF530 Total n=45	APF530 250 mg n=17	APF530 500 mg n=18	APF530 Total n=35
Any TEAE, %	76.5	80.0	92.3	82.2	58.8	44.4	51.4
Any serious TEAE, %	5.9	20.0	0	8.9	5.9	11.1	8.6
Constipation	5.9	20.0	23.1	15.6	23.5	5.6	14.3
Diarrhea	23.5	6.7	15.4	15.6	0	0	0
Headache	11.8	13.3	30.8	17.8	0	0	0
Fatigue	11.8	13.3	15.4	13.3	0	0	0
Anorexia	11.8	0	15.4	8.9	0	0	0
Weight loss	11.8	6.7	7.7	8.9	0	0	0
Dizziness	5.9	6.7	7.7	6.7	0	0	0
Anemia	0	20.0	0	6.7	5.9	11.1	8.9
Neutropenia	0	6.7	15.4	6.7	0	0	0
Mucosal inflammation	0	0	15.4	4.4	0	0	0
Peripheral edema	5.9	6.7	0	4.4	0	0	0
Dysgeusia	11.8	0	0	4.4	5.9	0	2.9
Chest wall pain	11.8	0	0	4.4	0	0	0
Dyspnea	0	6.7	7.7	4.4	0	0	0
Insomnia	5.9	0	7.7	4.4	0	0	0
Peripheral edema	5.9	6.7	0	4.4	5.9	0	2.9
DVT	5.9	0	0	2.2	0	0	0
Thrombocytopenia	0	0	7.7	2.2	0	11.1	5.7
Injection site reactions, %							
Erythema	17.7	6.7	0	8.9	5.9	5.6	5.7
Induration	11.8	6.7	0	6.7	5.9	11.1	8.6
Bruising	5.9	0	7.7	4.4	5.9	5.6	5.7
Pain	0	6.7	0	2.2	0	5.6	2.9

Abbreviations: DVT, deep vein thrombosis; TEAE, treatment-emergent adverse event.

Efficacy

Both acute-onset and delayed-onset CINV were controlled at all doses in both the US and European trials (Table 8). Among those treated with APF530 250 or 500 mg, CR was obtained in ≥83% of patients, in both the acute-onset and delayed-onset phases, and complete control was obtained in ≥76%, indicating that nausea was controlled almost as effectively as emesis; the nausea that did occur was mostly mild.

Discussion

The most important finding of these similarly designed Phase II trials was that granisetron exposure was maintained for 7 days with a single APF530 SC dose. In both studies, granisetron pharmacokinetics were similar and dose proportional with regard to the C_{max} achieved and drug exposure over the acute-onset (24 hours) and delayed-onset (168 hours) phases.

In C2005-01, six of the 45 enrolled patients violated protocol in that they received additional chemotherapy within 14 days after receiving APF530. In the judgment of the medical monitor, chemotherapy received after day 7 would not affect assessment of the primary (pharmacokinetics) objective or efficacy. However, chemotherapy administered from days 7 to 14 could have affected the assessment of AEs in the second week of the study. In C2007-01, six of 35 enrolled patients did not meet the study entry criteria because of their age or participation in another trial within 30 days; these were considered minor deviations unlikely to affect the study outcome.

The granisetron transdermal patch (Sancuso®) is another extended-release form of granisetron but is unlike APF530. It is designed to provide extended release of granisetron for up to 7 days. Unlike APF530, the patch is intended for use with multiday chemotherapy regimens and must be applied 24 to 48 hours before the start of chemotherapy because of the time (48 hours) required to reach the granisetron C_{max}. The C_{max} achieved with the patch is about half that achieved with APF530 250 mg, and the total exposure over 7 days (AUC at 0 to 168 hours) is comparable with that of APF530 250 mg.[10,11] Overall, the CR rate was 60% with the patch compared with 65% for oral granisetron.[11] Detachment of the patch reduces the amount of granisetron delivered and may be the cause of at least some of the broad variability noted in the pharmacokinetic measurements.[10]

Interpreting the findings with APF530 SC in the context of granisetron IV is not straightforward because a minimal

Table 8 Summary of responses to APF530 in both Phase II studies

Response	Period	APF530 250 mg		APF530 500 mg		APF530 750 mg		APF530 All	
		n/N	%	n/N	%	n/N	%	n/N	%
Study C2005-01									
Complete response	Acute-onset (0–24 h)	12/13	92.3	14/15	93.3	9/13	69.2	35/41	85.4
	Delayed-onset (>24–168 h)	12/13	92.3	10/12	83.3	7/12	58.3	29/37	78.4
	Overall (0–168 h)	11/13	84.6	6/12	75.0	6/12	50.00	26/37	70.3
Complete control	Acute-onset (0–24 h)	12/13	92.3	14/15	93.3	9/13	69.2	35/41	85.4
	Delayed-onset (>24–168 h)	12/13	92.3	10/13	76.9	9/13	50.0	28/38	73.7
	Overall (0–168 h)	11/13	84.6	9/13	69.2	5/12	41.7	25/38	65.8
Total response	Acute-onset (0–24 h)	10/13	76.9	14/15	93.3	8/13	61.5	32/41	78.1
	Delayed-onset (>24–168 h)	9/13	69.2	8/13	61.5	5/13	38.5	23/39	59.0
	Overall (0–168 h)	7/13	53.8	7/13	53.8	4/13	30.8	18/39	46.2
Study C2007-01*									
Complete response	Acute-onset (0–24 h)	16/17	94.1	16/18	88.9	–	–	32/35	91.4
	Delayed-onset (>24–168 h)	15/17	88.2	17/18	94.4	–	–	32/35	91.4
	Overall (0–168 h)	14/17	82.4	15/18	83.3	–	–	29/35	82.9
Complete control	Acute-onset (0–24 h)	15/17	88.2	16/18	88.9	–	–	31/35	88.6
	Delayed-onset (>24–168 h)	15/17	88.2	17/18	94.4	–	–	32/35	91.4
	Overall (0–168 h)	14/17	82.4	15/18	83.3	–	–	29/35	82.9
Total response	Acute-onset (0–24 h)	14/17	82.4	15/18	83.3	–	–	29/35	82.9
	Delayed-onset (>24–168 h)	14/17	82.4	17/18	94.4	–	–	31/35	88.6
	Overall (0–168 h)	12/17	70.6	14/18	77.8	–	–	26/35	74.3

Note: *Six patients in study C2007-01 received MEC: two in the 250 mg group, four in the 500 mg group.
Abbreviations: h, hours; MEC, moderately emetogenic chemotherapy.

effective concentration of granisetron in prevention of CINV has not been defined. The recommended dose of granisetron for prevention of CINV is 10 μg/kg,[12] which achieves a C_{max} of 4.9 ng/mL.[13] In an APF530 Phase I safety and pharmacokinetics study in normal volunteers in which granisetron IV (50 μg/kg) was used as a control, granisetron concentrations at 24 and 48 hours were 3.67 and 0.890 ng/mL, respectively. Assuming that an effective granisetron concentration is maintained for at least 48 hours, the minimal effective concentration is <1.0 ng/mL.[13] With APF530 500 mg in C2005-01, the granisetron concentration at 168 hours was 1.96 ng/mL; it appears that an effective concentration of granisetron was maintained over at least 7 days with APF530 500 mg.

The dose of granisetron in APF530 SC raised no safety issues. Regulatory concerns regarding potential prolongation of the QTc by 5-HT_3 inhibitors resulted in labeling changes regarding potential cardiac safety for granisetron.[14] The labeling change was based on individual incidents of QT prolongation.[12,15] However, no effect on QTc intervals had been seen in several earlier trials with IV and oral granisetron,[16–20] and a recent study with transdermal granisetron also reported no significant effects on QTc or other ECG variables.[13] The effect of high-dose APF530 on the QTc interval (QTc) was assessed in a blinded, placebo-controlled study in normal volunteers with APF530 SC 1,000 mg. No clinically significant QTc prolongation was seen with APF530 SC or granisetron IV.[8]

Based on the findings in these Phase II trials, a Phase III trial was conducted to assess the efficacy of APF530 SC 250 mg and APF530 SC 500 mg in comparison with the second-generation 5-HT_3 inhibitor palonosetron. For the 500 mg dose of APF530, the CR rate was noninferior to that of palonosetron in the control of acute emesis following administration of MEC or HEC, and in control of delayed emesis following administration of MEC. In control of delayed emesis following HEC, CR rates with APF530 SC 500 mg were numerically superior to those of palonosetron, although superiority to palonosetron in this setting was not demonstrated.[6,21]

Conclusion

The pharmacokinetic properties of APF530 have been defined in two Phase II trials in cancer patients receiving a MEC or a HEC regimen. An effective plasma concentration of granisetron was maintained for 7 days with a single dose of APF530. APF530 was well tolerated, exhibiting AEs expected with granisetron. Injection site reactions occurred in fewer than 10% of patients and were mild in most patients. Preliminary efficacy data suggest that APF530 is an expanded option for prevention of acute and delayed CINV. APF530 is a novel delivery system that could particularly benefit chemotherapy patients in the outpatient setting, where convenience and patient compliance are important concerns. On the basis of the findings in this

study, APF530 SC 250 mg and APF530 SC 500 mg were carried forward in a Phase III trial.

Author contributions

NG, RY, MS, and RB were the study site investigators, EO was the clinical representative, CS was the clinical study nurse at the Gabrail Cancer Center, and WC performed the statistical analysis. All authors were involved in study conception and design, data acquisition, and the drafting and critical revision of the manuscript's intellectual content. All authors have read and approved the final manuscript, and agree to be accountable for all aspects of the work's accuracy and integrity.

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