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ARTICLE

Pharmacokinetics and tolerability of apremilast in healthy Korean adult men

Ki Young Huh[1] | Yewon Choi[1] | Jim Nissel[2] | Maria Palmisano[2] | Xiaomin Wang[2] | Liangang Liu[2] | Francisco Ramirez-Valle[2] | Howard Lee[1,3,4,5]

[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Korea

[2]Bristol Myers Squibb Company, Summit – West, NJ, USA

[3]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea

[4]Center for Convergence Approaches in Drug Development, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea

[5]Advanced Institute of Convergence Technology, Suwon, Korea

Correspondence
Howard Lee, Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: howardlee@snu.ac.kr

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Abstract

We performed a two-part study to evaluate the pharmacokinetics, safety, and tolerability of oral apremilast, a phosphodiesterase 4 inhibitor indicated for the treatment of psoriasis, in healthy Korean adult men. In part 1, there were 12 subjects who randomly received a single oral dose of apremilast at 20, 30, or 40 mg in each of 3 periods in a crossover fashion. In part 2, there were 16 subjects who randomly received 30 mg of apremilast or its matching placebo in a ratio of 3:1 twice daily for 14 days. Apremilast was rapidly absorbed (maximum concentration: ~2–3 h postdose), and eliminated according to a monoexponential pattern with a terminal-phase elimination half-life of 8–9 h. The exposure to apremilast increased in a dose-proportional manner and accumulation was 1.6-fold at steady-state. Apremilast was well-tolerated after a single oral administration and multiple oral administrations in Korean adult men; all of the treatment-emergent adverse events were mild and recovered without sequelae. In conclusion, apremilast was safe and well-tolerated in healthy Korean adult men when administered single oral doses of 20, 30, or 40 mg or when administered multiple oral doses of 30 mg b.i.d. for 14 days. Overall exposures increased in an approximate dose proportional manner in healthy Korean adult men.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Apremilast, a phosphodiesterase 4 inhibitor, has been approved to treat patients with psoriasis in many countries, including the United States, Canada, and Japan. Although apremilast has shown a linear pharmacokinetic (PK) profile and little ethnic sensitivity, apremilast has never been studied specifically in Koreans.

WHAT QUESTION DID THIS STUDY ADDRESS?

This two-part study evaluated differences in PKs and tolerability of apremilast between healthy Korean adult men and previously studied ethnic populations.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Our results clearly showed that apremilast was safe and well-tolerated after single and multiple oral administrations in healthy Korean adult men. Linear PK profiles of apremilast were consistently observed in healthy Korean adult men.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Our results support the notion that recommended apremilast dose of 30 mg b.i.d., after a first week of titration, would be also appropriate in Koreans.

INTRODUCTION

Psoriasis is a chronic autoimmune inflammatory disease characterized by skin patches with various systemic manifestations.[1,2] Psoriasis is frequently comorbid with other diseases, such as arthritis, cardio-metabolic disease, gastrointestinal disease, mood disorders, and malignancies.[3] Approximately 0.04% to 0.19% of the total global disease burden is attributable to the skin manifestations of psoriasis,[4,5] which can be further increased by the comorbid nature of psoriasis.[6,7]

Apremilast, a phosphodiesterase 4 (PDE4) inhibitor, was approved to treat patients with psoriasis in many countries, including the United States, Canada, and Japan.[8,9] The recommended dosage regimen for apremilast is to give it orally twice daily at 30 mg after titration over a week,[8,10] which could ameliorate gastrointestinal symptoms of apremilast.[11] The maximum concentration (C_{max}) of apremilast was attained in 2.5–3.5 h after oral administration consistently across healthy Japanese, Chinese, and White male subjects.[12] Apremilast is metabolized primarily by cytochrome P450 3A4 (CYP3A4),[13] and dose adjustment is not required in patients with hepatic impairment.[8,14] It is noteworthy that the pharmacokinetic (PK) characteristics of apremilast were similar irrespective of ethnicity.[12] The lack of ethnic sensitivity in the PK of apremilast may render it similar efficacy among those ethnic groups because apremilast showed a dose-response relationship.[12]

However, the PK characteristics of apremilast have not been investigated in Koreans. The objective of this study was to evaluate the PKs, safety, and tolerability profiles of oral apremilast in healthy Koreans. To this end, we conducted a single dose crossover PK safety study and a multiple dose PK safety study with apremilast in healthy Korean adult men. Dose titration recommended in the approved regimen was not instituted to maximize comparability to previous PK studies.

METHODS

Study subjects

Korean men 18–45 years of age with a body mass index (BMI) of 18–30 kg/m^2 were eligible if they had no clinically significant abnormality in medical interview, physical examinations, vital signs, 12-lead electrocardiogram (ECG), or clinical laboratory tests. Written informed consent was obtained from eligible subjects prior to any study-related procedure performed. This study was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea, and conducted in full accordance with the Declaration of Helsinki (ClinicalTrials.gov registration no.: NCT02802735).

Study design

This study consisted of two parts (Figure 1). Part 1 was a randomized, open-label, 3-period, 3-treatment, 3-sequence crossover study in 12 subjects. Eligible subjects were randomized to receive a single oral dose of apremilast at 20, 30, and 40 mg in each period according to the sequence they were assigned to after a washout of greater than or equal to 7 days between the 2 adjacent periods. Blood samples for PK analysis were obtained at 0 (i.e., predose), 0.5, 1, 1.5, 2, 3, 5, 8, 12, 24, 36, 48, 60, and 72 h postdose. Part 2 was a randomized, double-blind, placebo-controlled, multiple-dose study, where 16 subjects were administered 30 mg of apremilast orally or its matching placebo twice a day for 14 days in a ratio of 3:1. Blood samples for PK analysis were collected 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 5, 8, and 12 h postdose on days 1 and 14. Additional samples were obtained on day 14 at 24, 36, 48, 60, and 72 h postdose. Furthermore, predose PK samples were collected on days 3, 5, 9, and 13 to see if steady-state was achieved.

Bioanalytical assay

Each PK sample was centrifuged at 1500 *g* for 10 min at 4°C and stored below −20°C. Concentrations of apremilast in plasma were determined using a validated liquid chromatography tandem mass spectrometry assay. The calibration range for apremilast was 1.00 (lower limit of quantification) to 1000 ng/ml. The intra-day accuracy and precision ranged −1.6 to 4.6 and 0.8 to 3.3 (expressed as a percentage of relative error), respectively. The inter-day counterparts ranged −0.2 to 3.5 and 0.0 to 2.6, respectively.

Pharmacokinetic analysis

The PK parameters of apremilast were derived using a noncompartmental method implemented in the Phoenix WinNonlin (Version 8.1; Certara USA, Princeton, NJ). The C_{max} and the time to reach C_{max} (T_{max}) were determined directly from the observed values. The area under the plasma concentration-time curve (AUC) from time zero to the last observable concentration (AUC_t) and AUC

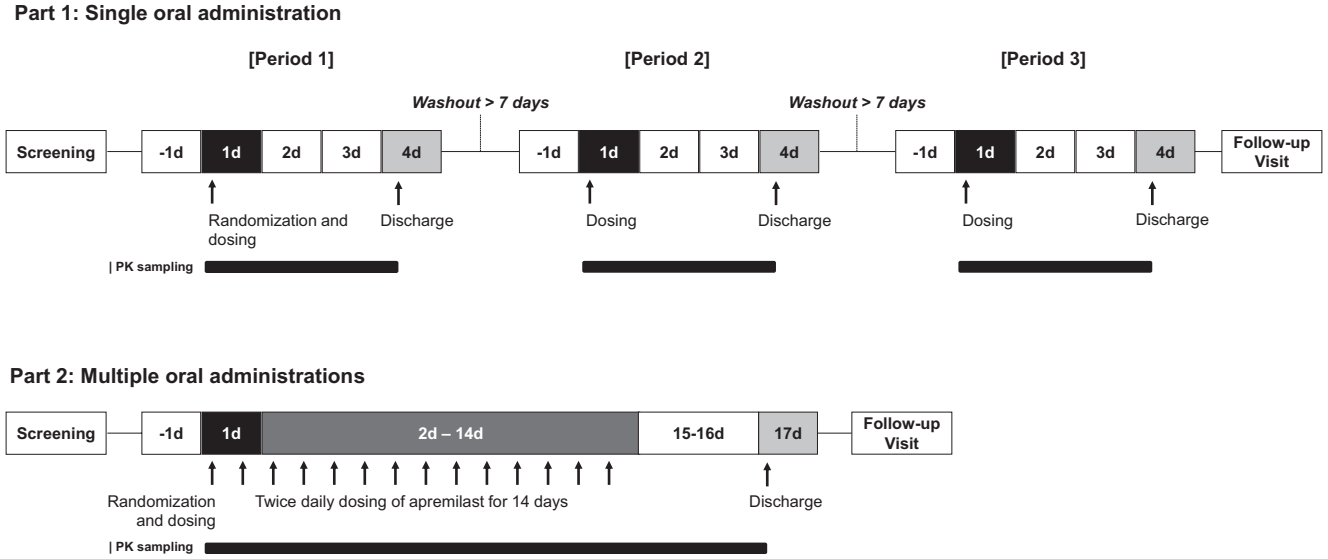

FIGURE 1 Schematic representation of study design. PK, pharmacokinetic

over a dosing interval at steady state (AUC_τ) were calculated using the linear trapezoidal method. AUC from time zero to infinity (AUC_{inf}) was calculated as $AUC_t + C_t/\lambda_z$, where C_t is the last measurable concentration and λ_z is terminal elimination constant estimated by linear regression. The accumulation ratio was AUC_τ divided by AUC over a dosing interval (i.e., 12 h) on day 1.

Safety and tolerability

Safety was monitored throughout the study using adverse event reporting from subjects, physical examinations, vital sign measurements, 12-lead ECGs, clinical laboratory safety tests, and review of concomitant medications and procedures.

Statistical analysis

Baseline demographics, PKs, safety, and tolerability data were summarized using descriptive statistics. The Kruskal-Wallis test was used for dose-normalized AUCs and C_{max} between dose groups in part 1 to evaluate dose-proportionality. The SAS software (version 9.3; SAS Institute, Inc., Cary, NC) was used for statistical analyses, and a p value less than or equal to 0.05 was considered statistically significant.

RESULTS

Subject disposition and demographics

A total of 28 subjects were enrolled, of whom 27 subjects (11 and 16 subjects in parts 1 and 2, respectively) completed the study as planned. One subject in part 1 withdrew the consent before the third period. The demographic characteristics were similar between treatment sequences (part 1) and treatment groups (part 2), and between parts 1 and 2 (Table 1).

Pharmacokinetics

Apremilast was rapidly absorbed and reached C_{max} at ~2–3 h after a single oral administration (Table 2). Apremilast was eliminated according to a monoexponential pattern with a terminal-phase elimination half-life of 8–9 h. Apremilast showed a linear PK profile after a single oral administration; neither the dose-normalized C_{max} (p value = 0.5220, Kruskal-Wallis test) nor the AUC_{inf} (p value = 0.3146, Kruskal-Wallis test) was significantly different between doses.

Apremilast was accumulated 1.6-fold at steady-state after twice daily oral administration at 30 mg (Table 2). Apremilast reached steady-state on the fifth day after twice daily oral administration (Figure S1). Apremilast PK parameters, other than C_{max} and AUC, were comparable between single and multiple doses. For example, the mean apparent clearance was 11.1–12.7 L/h and 11.5 L/h, respectively, after a single oral administration and at steady-state (Table 2).

Safety and tolerability

Neither death nor serious adverse events were reported during and after the study. A total of 14 subjects experienced 31 treatment-emergent adverse events (TEAEs); 10 subjects

TABLE 1 Baseline demographic characteristics of subjects

	Part 1 (single oral administration)				Part 2 (multiple oral administrations)			
Treatment	**ABC (*N* = 4)**	**BCA (*N* = 4)**	**CAB (*N* = 4)**	**Total (*N* = 12)**	**30 mg b.i.d. (*N* = 12)**	**Placebo (*N* = 4)**	**Total (*N* = 16)**	**Total (*N* = 28)**
Sex								
Male	4 (100)	4 (100)	4 (100)	12 (100)	12 (100)	4 (100)	16 (100)	28 (100)
Ethnicity								
Asian	4 (100)	4 (100)	4 (100)	12 (100)	12 (100)	4 (100)	16 (100)	28 (100)
Age, years	34.0 [25.0–43.0]	26.8 [25.0–29.0]	28.8 [19.0–36.0]	29.8 [19.0–43.0]	30.8 [24.0–41.0]	25.5 [20.0–31.0]	29.5 [20.0–41.0]	29.6 [19.0–43.0]
Height, cm	170.4 [161.6–178.8]	176.7 [170.2–185.8]	171.1 [166.2–175.1]	172.8 [161.6–185.8]	174.7 [151.5–186.7]	169.9 [163.1–178.3]	173.5 [151.5–186.7]	173.1 [151.5–186.7]
Weight, kg	71.9 [62.1–83.5]	78.0 [66.4–88.9]	71.8 [62.2–86.4]	73.9 [62.1–88.9]	73.7 [56.7–95.1]	71.5 [58.1–89.5]	73.1 [56.7–95.1]	73.5 [56.7–95.1]
BMI, kg/m^2	24.8 [21.5–29.1]	25.0 [22.8–28.3]	24.4 [22.5–28.2]	24.7 [21.5–29.1]	24.1 [18.6–27.8]	24.8 [20.2–29.8]	24.3 [18.6–29.8]	24.5 [18.6–29.8]

Note: The number of subjects (percentage of subjects) was presented for sex and ethnicity whereas mean [minimum-maximum] for other variables. Treatment groups were presented as the sequence of the treatments at each period in part 1.

Abbreviations: BMI, body mass index; A, single oral administration of apremilast 20 mg; B, single oral administration of apremilast 30 mg; C, single oral administration 40 mg; 30 mg b.i.d., multiple oral administrations of apremilast 30 mg twice daily for 14 days.

experienced 17 TEAEs that were considered related to study medication (Table 3). All of the TEAEs were mild in severity and recovered without sequelae. No subject was dropped out due to a TEAE.

Multiple administrations of apremilast were associated with a greater frequency of TEAEs related to study medication than that after a single administration (Table 3). Diarrhea and nausea were consistently reported both after single or multiple administrations of apremilast, whereas they were not reported in subjects who received placebo. Higher doses of apremilast were associated with more frequent diarrhea. Dermatological events, such as rash, pruritus, skin exfoliation, and headaches, were only reported after multiple administrations of apremilast or placebo; however, the proportion of subjects were the same to that in the placebo group (25.0%; Table 3).

DISCUSSION

Apremilast has exhibited linear PK characteristics in multiple studies. Apremilast was rapidly absorbed not only in healthy White and Black subjects,[15,16] but in healthy Japanese and Chinese subjects as well.[12] In addition, apremilast demonstrated a linear PK profile after a single oral administration[9]; C_{max} and AUCs increased linearly after single and multiple oral administrations of apremilast up to 80 mg once daily or 50 mg twice daily.[12]

The PK characteristics of apremilast in Koreans, as we showed in this study, were comparable to those reported in the previous studies. We showed that apremilast was rapidly and steadily absorbed and its systemic exposure was increased in a dose-proportional manner in healthy Korean adult men. The evidence is that the maximum apremilast concentration was consistently reached within 3 h after single and multiple oral administrations (Table 2, Figures 2 and 3). Additionally, the dose-normalized C_{max} and AUCs were not statistically different between doses. Furthermore, steady-state was achieved with minimal accumulation, consistent with the known accumulation ratio of 1.0–1.5 when given once daily.[12]

The results of our study support the lack of interethnic difference in apremilast PK.[12] Because multiple pathways are involved in the metabolism of apremilast,[17] ethnicity is less likely to play a significant role in the elimination of apremilast.[17-19] This suggests PK profiles in Koreans might be similar to those in other ethnicities, although direct comparison was not possible due to the design of the study.

Based on our results, and taking into account available data on apremilast PK,[12] the recommended apremilast dose and regimen is 30 mg twice daily administered orally,[20] after the first week of titration, seems appropriate for all different ethnicities tested, including Koreans. Apremilast

TABLE 2 Summary pharmacokinetics parameters of apremilast

	Part 1 (single oral administration)			Part 2 (multiple oral administrations)	
	20 mg ($N = 11$)	30 mg ($N = 12$)	40 mg ($N = 12$)	30 mg b.i.d. ($N = 12$) on the first day	30 mg b.i.d. ($N = 12$) at steady-state (14th day)
C_{max}, ng/ml	205 (32.1)	273 (32.1)	373 (19.7)	283 (34.3)	408 (36.5)
T_{max}, h[a]	3.0 [1.5–5.0]	3.0 [1.5–5.0]	2.0 [0.5–5.0]	2.0 [1.0–5.0]	1.5 [1.0–3.0]
AUC_t, ng h/ml	1770 (25.8)	2330 (22.6)	3470 (25.7)		
AUC_τ, ng h/ml				1610 (33.0)	2600 (34.3)
AUC_{inf}, ng h/ml	1790 (25.5)	2360 (22.1)	3500 (25.6)		
$t_{1/2}$, h	7.4 (35.2)	8.2 (44.4)	7.4 (36.8)		7.80 (31.4)
CL/F, L/h	11.1 (25.5)	12.7 (22.1)	11.4 (25.6)		11.5 (34.3)
V_z/F, L	120 (47.6)	151 (49.6)	122 (38.7)		130 (53.3)
Accumulation ratio					1.62 (36.0)

Note: Data were presented as geometric mean (geometric coefficient of variation) except for T_{max}, for which median [minimum-maximum] was presented.

Abbreviations: AUC, area under the plasma concentration-time curve; AUC_{inf}, AUC from time zero to infinity; AUC_τ, AUC over a dosing interval at steady state; AUC_t, AUC from time zero to the last observable concentration; CL/F, apparent clearance of drug from plasma after extravascular administration; C_{max}, maximum plasma concentration; $t_{1/2}$, terminal-phase elimination half-life; T_{max}, time to reach C_{max}; V_z/F, apparent volume of distribution during the terminal phase after extravascular administration.

TABLE 3 Summary of treatment-emergent adverse events related to study medication

	Part 1 (single oral administration)				Part 2 (multiple oral administrations)			
System organ class preferred term	20 mg ($N = 11$)	30 mg ($N = 12$)	40 mg ($N = 12$)	Total ($N = 12$)	30 mg b.i.d. ($N = 12$)	Placebo ($N = 4$)	Total ($N = 16$)	Overall total ($N = 28$)
Gastrointestinal disorders	1 (9.1)	1 (8.3)	2 (16.7)	2 (16.7)	2 (16.7)		4 (14.3)	4 (14.3)
Diarrhea	1 (9.1)	1 (8.3)	1 (8.3)	1 (8.3)	2 (16.7)		3 (10.7)	3 (10.7)
Nausea			1 (8.3)	1 (8.3)			1 (3.6)	1 (3.6)
Skin and subcutaneous tissue disorders					3 (25.0)	1 (25.0)	4 (14.3)	4 (14.3)
Rash					1 (8.3)	1 (25.0)	2 (7.1)	2 (7.1)
Pruritus					1 (8.3)		1 (3.6)	1 (3.6)
Rash popular					1 (8.3)		1 (3.6)	1 (3.6)
Skin exfoliation					1 (8.3)		1 (3.6)	1 (3.6)
Nervous system disorders					3 (25.0)	1 (25.0)	4 (14.3)	4 (14.3)
Headache					3 (25.0)	1 (25.0)	4 (14.3)	4 (14.3)
Musculoskeletal and connective tissue disorders					1 (8.3)		1 (3.6)	1 (3.6)
Myalgia					1 (8.3)		1 (3.6)	1 (3.6)
Total number of subjects	1 (9.1)	1 (8.3)	2 (16.7)	2 (16.7)	6 (50.0)	2 (50.0)	8 (50.0)	10 (35.7)

Note: The proportion (%) of subjects who experienced adverse drug reaction in each group are presented in the parentheses.

demonstrated dose-response relationship[21] and response to apremilast is generally similar between different ethnicities.[22,23] Furthermore, the epidemiology and clinical manifestation of psoriasis in Korean patients were not significantly different from those in other ethnic groups.[24] Additionally, apremilast was also safe and well-tolerated in healthy Korean adult men.

Our study had limitations. Extrapolating the results to patients with psoriasis might be limited because this study was conducted in healthy subjects. The sample size was also small. Nevertheless, the results of our study were useful to evaluate the PKs, safety, and tolerability of apremilast in Koreans.

In conclusion, apremilast was safe and well-tolerated in healthy Korean adult men when administered single doses of

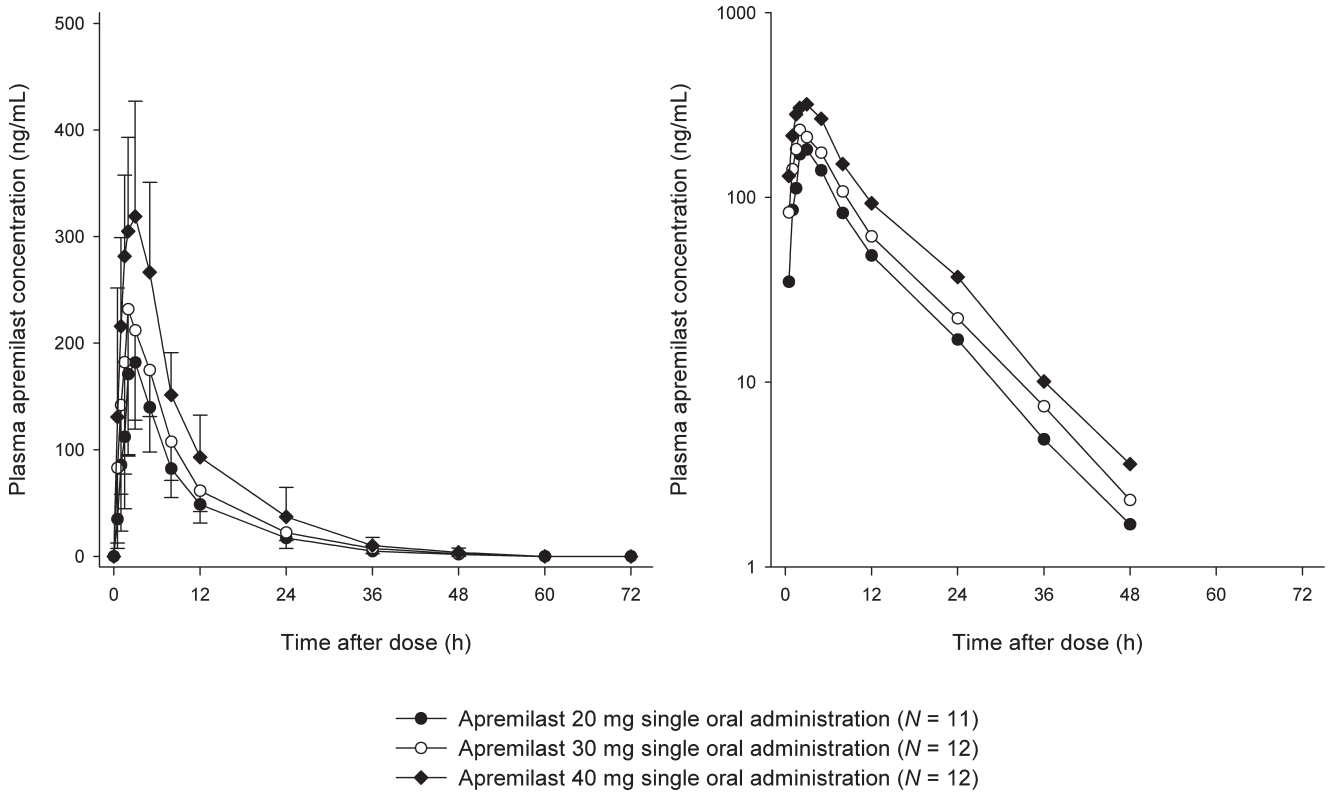

FIGURE 2 Mean plasma apremilast concentration-time curves after a single oral administration at 20, 30, and 40 mg (left: linear scale, right: semi-logarithmic scale). The error bars denote the SDs

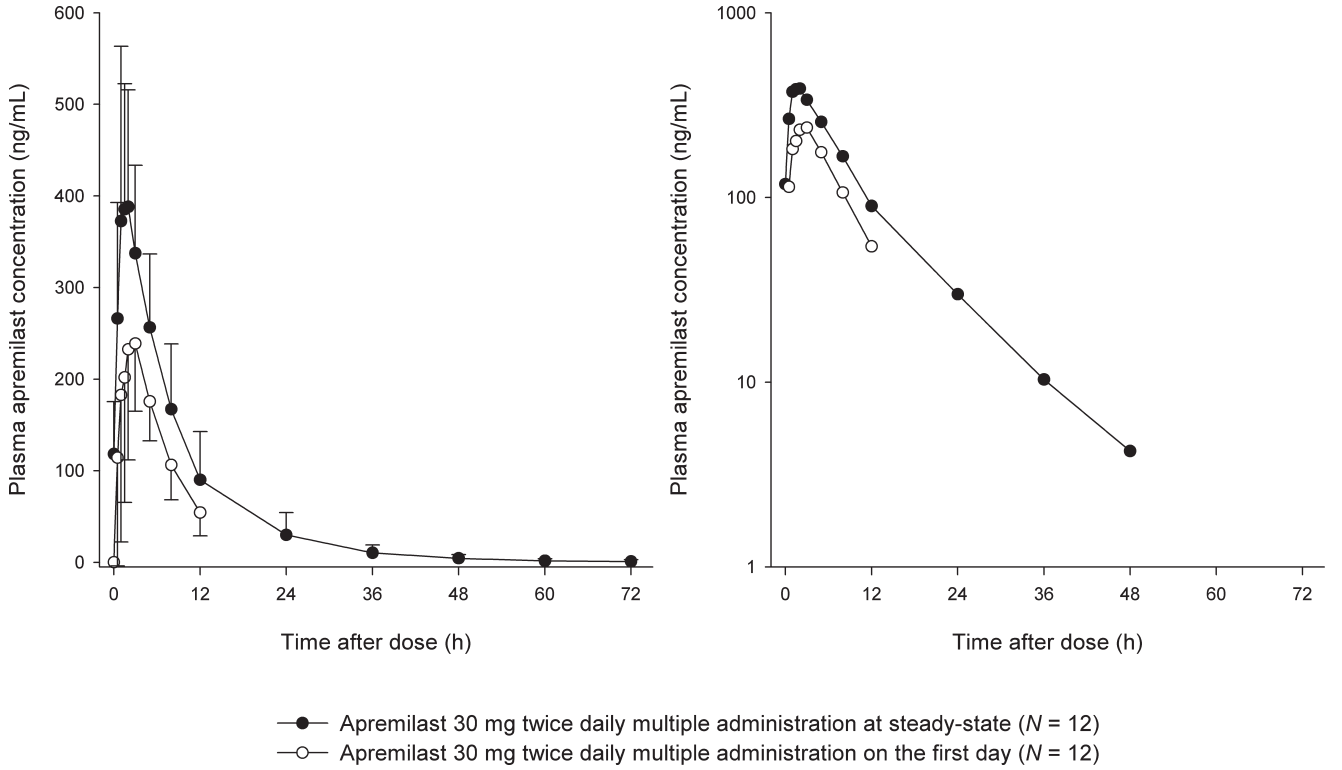

FIGURE 3 Mean plasma apremilast concentration-time curves after multiple administration at 30 mg twice daily: first day versus steady-state (left: linear scale, right: semi-logarithmic scale). The error bars denote the SDs

20, 30, or 40 mg or when administered multiple oral doses of 30 mg b.i.d. for 14 days. Overall exposures increased in an approximate dose proportional manner in healthy Korean adult men.

CONFLICT OF INTEREST

J.N., M.P., X.W., L.L., and F.R.-V. are employees of Bristol Myers Squibb Company. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

K.Y.H. and H.L. wrote the manuscript. Y.C., L.L., F.R., and H.L. designed the research. Y.C., J.N., M.P., X.W., F.R., and H.L. performed the research. K.Y.H., Y.C., J.N., X.W., L.L., F.R., and H.L. analyzed data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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