Transl Clin Pharmacol. 2022 Sep;30(3):136-144
https://doi.org/10.12793/tcp.2022.30.e13
pISSN 2289-0882·eISSN 2383-5427

Translational and Clinical Pharmacology TCP

Original Article

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A randomized, open-label, single-dose, two-way crossover study to assess the pharmacokinetics between two tablets of fixed-dose combination formulation with raloxifene and cholecalciferol and concomitant administration of each agents in healthy male volunteers

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Received: Jun 23, 2022
Revised: Aug 31, 2022
Accepted: Sep 13, 2022
Published online: Sep 15, 2022

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ABSTRACT

A new fixed-dose combination (FDC) formulation of raloxifene 60 mg and cholecalciferol 800 IU was developed to improve the medication compliance and overall efficacy of raloxifene treatment in postmenopausal osteoporosis patients. The aim of this study was to compare the pharmacokinetics between two tablets of FDC formulation of raloxifene/cholecalciferol and the two products administered concomitantly at respective doses. This randomized, open-label, single-dose, two-treatment, two-way crossover study included 46 volunteers. During each treatment period, subjects received the test formulation (FDC formulation containing raloxifene and cholecalciferol) or the reference formulation (co-administration of raloxifene and cholecalciferol), with a 14-d washout period. Serial blood samples were collected periodically over 96 hours after drug intake. In total, 46 subjects completed the study. The geometric mean ratios and its 90% confidence intervals of the FDC to the single agents for the area under the concentration-time curve from zero to the last quantifiable time point and the maximum plasma concentration met the regulatory criteria for bioequivalence: 1.1364 (1.0584–1.2201) and 1.1010 (0.9945–1.2188) for raloxifene and 1.0266 (0.9591–1.0989) and 1.0354 (0.9816–1.0921) for baseline-corrected cholecalciferol, respectively. Both formulations were well tolerated. No significant differences was observed in the incidence of adverse events between the two treatments. It was concluded that two tablets of the newly developed FDC formulation of raloxifene and cholecalciferol and the corresponding two agents administered concomitantly at respective doses were bioequivalent.

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Funding
This study was sponsored by Alvogen Korea Co. Ltd., Seoul, Republic of Korea, and was supported by the grants from the Korea Health technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI14C2750) as well as by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2020R1I1A1A01064906).

Trial Registration
ClinicalTrials.gov Identifier: NCT03010267

Conflict of Interest
B. L. is an employee of Alvogen Korea Co. Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article. The sponsor did not participate in the execution of the study or analysis of the data.

Author Contributions
Conceptualization: Lee HW; Data curation: Kang WY, Seong SJ; Formal analysis: Lee HS, Seong SJ; Investigation: Kang WY, Lee HW; Choi EJ; Methodology: Kang WY, Lee HW; Kim EH; Cho K; Resources: Gwon MR; Lee B; Supervision: Yoon YR; Writing - original draft: Lee HW, Kang WY; Writing - review & editing: Yoon YR, Seong SJ.

Trial Registration: ClinicalTrials.gov Identifier: NCT03010267

Keywords: Osteoporosis; Pharmacokinetics; Raloxifene; Cholecalciferol

INTRODUCTION

Osteoporosis is a metabolic bone disease characterized by low bone mass and impaired microarchitecture of bone tissue, with a consequent increase in the risk of fragility fracture, leading to pain, disability, and mortality [1,2]. Osteoporosis predominantly affects postmenopausal women, burdening the affected individual and society.

Raloxifene hydrochloride, a second-generation selective estrogen receptor modulator, has selective agonistic activities on bone and cholesterol metabolism and antagonistic activities in the uterine or breast tissues [3,4]. This drug reduces bone resorption and turnover, leading to increased bone mineral density. Raloxifene is used as a first-line drug to treat and prevent osteoporosis in postmenopausal women [5]. In 3,204 postmenopausal women with osteopenia or osteoporosis, raloxifene 60 mg administered once daily for 3 years significantly decreased the risk of new vertebral fractures compared to that in the placebo group [6]. After 48 weeks of treatment in postmenopausal osteopenic women, raloxifene significantly increased the spine bone mineral density by 2.0%, compared to −1.1% with no treatment [7].

Cholecalciferol (vitamin D_3) plays an important role in maintaining blood calcium and phosphorus levels by increasing intestinal absorption of dietary calcium and phosphorus, promoting tubular reabsorption of calcium by the kidney, and increasing osteoclastic resorption [8,9]. Cholecalciferol is metabolically activated in the liver and the kidney to yield 1α, 25-$(OH)_2$ D_3 (calcitriol), the biologically active form of vitamin D_3. Accordingly, maintaining adequate blood concentrations of the biologically active vitamin D_3 is essential for bone metabolism and increased therapeutic effect in osteoporosis patients. However, vitamin D_3 supplementation, either by sunlight exposure or diet, is limited, leading to inadequate vitamin D, especially among postmenopausal women and osteoporosis patients [10].

Recent studies indicate that adding vitamin D supplements to maintain adequate vitamin D status shows an incremental benefit in patients treated for osteoporosis [11,12]. A fixed-dose osteoporosis treatment containing vitamin D_3 in a single pill can significantly improve medication compliance and therapeutic convenience and, consequently, increase the effectiveness of therapies in osteoporotic patients who require extra vitamin D. A fixed-dose combination (FDC) formulation of raloxifene and cholecalciferol 60 mg/800 IU has been developed by a pharmaceutical company in the Republic of Korea. The objective of this study was to compare the pharmacokinetic (PK) characteristics and determine bioequivalence between the test formulation (DP-R213; a 60 mg raloxifene/800 IU cholecalciferol FDC tablet; Alvogen Korea Co. Ltd., Seoul, Korea) and reference formulations (Evista® 60 mg; Takeda Pharmaceuticals Korea, Seoul, Korea; & Cholecalciferol 800 IU; Alvogen Korea Co. Ltd.) in healthy Korean volunteers.

https://doi.org/10.12793/tcp.2022.30.e13

METHODS

Subjects

Eligible subjects enrolled in the study were healthy Korean male volunteers (age: > 19 years, weight: ≥ 50 kg and within ± 20% of ideal body weight). The volunteers' health was assessed using clinical history, detailed physical examination, routine clinical laboratory tests, and 12-lead electrocardiography. Volunteers were not enrolled if they had a history of hypersensitivity to raloxifene or cholecalciferol; clinically significant medical history; abnormal laboratory findings for creatinine clearance, aspartate aminotransferase, alanine aminotransferase, or total bilirubin; a history of hypercalcemia, hypercalciuria, or renal stone; serum calcium levels > 1.2 times the upper normal limit or urinary calcium/creatinine ratio > 0.2; untreated hypocalcemia (serum calcium levels < 7.0 mg/dL); received a high dose of vitamin D3 (> 50,000 IU) within 1 month before the initiation of the study; or taking any prescription medications, herbal medications, over-the-counter drugs, or vitamin supplements within 10 days before the first dose.

Subjects were asked to shield themselves from direct sunlight exposure by completely covering themselves with clothes and a hat and applying sunscreen (SPF ≥ 30) when anticipating exposure to direct sunlight for ≥ 1 hour for 10 days before the first dose and throughout the study. Subjects were required to avoid foods with high vitamin D contents, vitamin D-fortified foods, and vitamin D supplements for at least 10 days before the first dose.

The study was conducted at Kyungpook National University Hospital (KNUH) Clinical Trial Center after the protocol was approved by the Institutional Review Board of KNUH and the Korea Ministry of Food and Drug Safety, in accordance with the ethical standards of the Declaration of Helsinki and its revisions, the International Conference on Harmonization's Good Clinical Practice, and local laws and regulations. All participants received written and oral information on the study and provided written informed consent before participation.

Study design

This study was a Phase I, open-label, randomized, single-dose, two-way crossover study in healthy subjects (ClinicalTrials.gov identifier: NCT03010267). Subjects who met all of the inclusion and none of the exclusion criteria were randomly allocated to one of two sequences, in which the treatments consisted of a single oral dose of two tablets of raloxifene/cholecalciferol (60 mg/800 IU) FDC (DP-R213) or co-administration of two tablets of each agents (raloxifene 60 mg and cholecalciferol 800 IU, respectively).

The subjects were hospitalized at the clinical trial center on day –1. On day 1, each study drug was administered with 150 mL of water following an overnight fast. The subjects who had completed the PK sampling for 96 hours and all safety evaluations were discharged. The subjects underwent a 14-d washout period between doses.

Analysis of raloxifene and cholecalciferol concentrations in plasma

Blood samples were collected before dosing (–24, –16, –8, and 0 hours) and at 1, 2, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72, and 96 hours after dosing to determine plasma concentrations of raloxifene and cholecalciferol. Each sample was collected in EDTA-K2 tubes. Plasma was obtained by centrifugation at 1,600×*g* for 10 minutes at 4°C, immediately transferred to four amber polypropylene tubes (1 mL each), and frozen at –70°C before analysis at the analytical laboratory, Biocore Co. Ltd. (Seoul, Korea).

https://doi.org/10.12793/tcp.2022.30.e13

Plasma concentrations of raloxifene and cholecalciferol were analyzed using validated bioanalytical methods. These methods consisted of liquid–liquid extraction for raloxifene and protein precipitation and solid-phase extraction for cholecalciferol, followed by quantification using ultra-fast liquid chromatography (UFLC) using a Shimadzu UFLC system (Shimadzu Corp., Kyoto, Japan). Tandem mass spectrometry was conducted using a TQ 5500 mass spectrometer (SCIEX, Foster City, CA, USA) for molecule ionization.

The calibration curves ranged from 10 to 1,500 pg/mL for raloxifene ($r \geq 0.9977$) and from 0.1 to 10 ng/mL ($r \geq 0.9978$) for cholecalciferol. The accuracy ranged from 96.9% to 101.4% for raloxifene and 102.5% to 107.9% for cholecalciferol; the coefficients of variation (CVs) were 2.6–5.6% for raloxifene and 4.9–12.4% for cholecalciferol. The lower limits of quantification were 10 pg/mL for raloxifene and 0.1 ng/mL for cholecalciferol.

PK analysis

PK parameters of raloxifene and cholecalciferol calculated by the standard non-compartmental analysis with Phoenix WinNonlin software version 6.3 (Pharsight Corporation, St. Louis, MO, USA) were as follows: maximum plasma concentration (C_{max}); time to reach C_{max} (t_{max}); area under the plasma concentration-time curve (AUC) from time 0 to the last measurement (AUC_{0-t}); AUC from 0 to infinity ($AUC_{0-\infty}$); apparent elimination half-life ($t_{1/2}$).

Sample size estimation

The sample size calculation for the study was based on the within-subject coefficient of variation values for AUC_{0-t} and C_{max} from previous studies (25.2% and 32.6%, respectively; unpublished data, Alvogen Korea Co. Ltd). A total of 19 subjects per group was required for the study to detect a 20% difference in the log-transformed PK parameters between the treatments at a 5% significance level and a power of 80%. To allow for dropouts, 46 subjects (23 subjects per group) were enrolled in the study.

Statistical analyses

Statistical analyses, including GMRs with 90% confidence intervals (CIs), were performed using the SAS software (ver. 9.2; SAS Institute Inc., Cary, NC, USA).

Demographic variables and PK parameters were analyzed by treatment group and summarized using descriptive statistics. Plasma concentration values below the limit of quantification of the assay were treated as zero. Primary PK parameters were C_{max} and AUC_{0-t} of raloxifene and cholecalciferol (baseline-corrected). Bioequivalence of raloxifene and cholecalciferol delivered via different formulations (FDC vs. individual agents) was established if the 90% CIs for the GMR of the primary PK parameters were within a predetermined range of 0.8000–1.2500.

Safety and tolerability evaluation

Safety and tolerability assessments were conducted throughout the study, based on the evaluation of clinical and laboratory adverse events (AEs), including subjective symptoms, vital signs, physical examinations, and 12-lead electrocardiograms. Subjects who received the study drugs at least once throughout the study period were included in the safety and tolerability assessment.

https://doi.org/10.12793/tcp.2022.30.e13

RESULTS

Subjects

In total, 69 volunteers were screened, and 48 male subjects satisfying the inclusion/exclusion criteria were enrolled in the study. Before dosing in period I, two subjects withdrew consent. Thus, 46 subjects who received at least one dose of raloxifene/ cholecalciferol and completed the study were included in the PK analyses and the safety assessment. The demographics of 46 subjects who completed the study are presented in **Table 1**.

PK data

The PK parameters of raloxifene and baseline-corrected cholecalciferol after administration of raloxifene 120 mg and cholecalciferol 1,600 IU as FDC or single agents concomitantly are listed in **Table 2**. The mean (SD) plasma concentration versus time profiles of raloxifene and baseline-corrected cholecalciferol following administration of raloxifene 120 mg and cholecalciferol 1,600 IU are given in **Fig. 1**.

As presented in **Table 3**, the GMR (90% CI) of AUC_{0-t} and C_{max} was 1.1364 (1.0584–1.2201) and 1.1010 (0.9945–1.2188) for raloxifene and 1.0266 (0.9591–1.0989) and 1.0354 (0.9816–1.0921) for baseline-corrected cholecalciferol, respectively, indicating that the 90% CIs of the PK parameters of raloxifene and baseline-corrected cholecalciferol fell within the bioequivalence criteria (0.8000 to 1.2500).

Table 1. Demographics of study subjects who completed the study according to sequence groups

Variables	Overall (n = 46)	Group 1 (n = 23)	Group 2 (n = 23)	*p*-value*
Age (yr)	26.5 ± 5.5 (19–50)	26.0 ± 6.2 (19–50)	27.0 ± 4.8 (22–36)	0.4328†
Height (cm)	174.8 ± 5.7 (158.2–189.4)	175.7 ± 5.9 (164.6–189.4)	173.9 ± 5.6 (158.2–182.9)	0.2955‡
Weight (kg)	69.1 ± 8.3 (50.6–86.4)	69.7 ± 8.2 (50.6–86.4)	68.5 ± 8.6 (56.4–86.1)	0.6289‡

Data are given as the mean ± standard deviation (range).
Group 1, RT; Group 2, TR; R, co-administration of two tablets of raloxifene 60 mg and cholecalciferol 800 IU; T, two tablets of fixed dose combination formulation of raloxiefene 60 mg and cholecalciferol 800 IU.
*Compared between two groups by Mann-Whitney *U* test† or independent *t*-test‡.

Table 2. Pharmacokinetic parameters of raloxifene and cholecalciferol following administration of raloxifene 120 mg and cholecalciferol 1,600 IU as a fixed-dose combination versus separate agents under fasted conditions in healthy male subjects (n = 46)

Pharmacokinetic parameters	FDC	Separate agents	*p*-value*
Raloxifene			
AUC_{0-t}, ng×h/mL	25.21 ± 8.12	22.49 ± 8.29	0.0048†
$AUC_{0-\infty}$, ng×h/mL	33.03 ± 31.38	25.97 ± 11.49	0.0320‡
C_{max}, ng/mL	0.72 ± 0.32	0.64 ± 0.26	0.0888†
$t_{1/2}$, h	33.90 ± 58.85	26.87 ± 17.41	0.2313‡
t_{max}, h§	10.0 (1.0–48.0)	7.0 (1.0–24.0)	0.3495‡
Baseline-corrected cholecalciferol			
AUC_{0-t}, ng×h/mL	71.29 ± 22.09	68.80 ± 21.08	0.2926†
$AUC_{0-\infty}$, ng×h/mL	75.30 ± 21.05	72.17 ± 21.38	0.2211†
C_{max}, ng/mL	2.66 ± 0.59	2.56 ± 0.56	0.2008†
$t_{1/2}$, h	14.37 ± 3.31	14.71 ± 3.37	0.8006‡
t_{max}, h§	12.0 (7.0–12.0)	10.0 (7.0–12.0)	0.8989‡

Data are presented as arithmetic means ± standard deviation, except for t_{max} values§ as median (range).
FDC, fixed dose combination; AUC_{0-t}, area under the plasma concentration versus time curve from time 0 to the last quantifiable time point; $AUC_{0-\infty}$, area under the plasma concentration versus time curve from time 0 to infinity; C_{max}, maximum plasma concentration; $t_{1/2}$, elimination half-life; t_{max}, time to reach C_{max}.
*Compared between two groups by paired *t*-test† or Wilcoxon signed rank test‡.

https://doi.org/10.12793/tcp.2022.30.e13

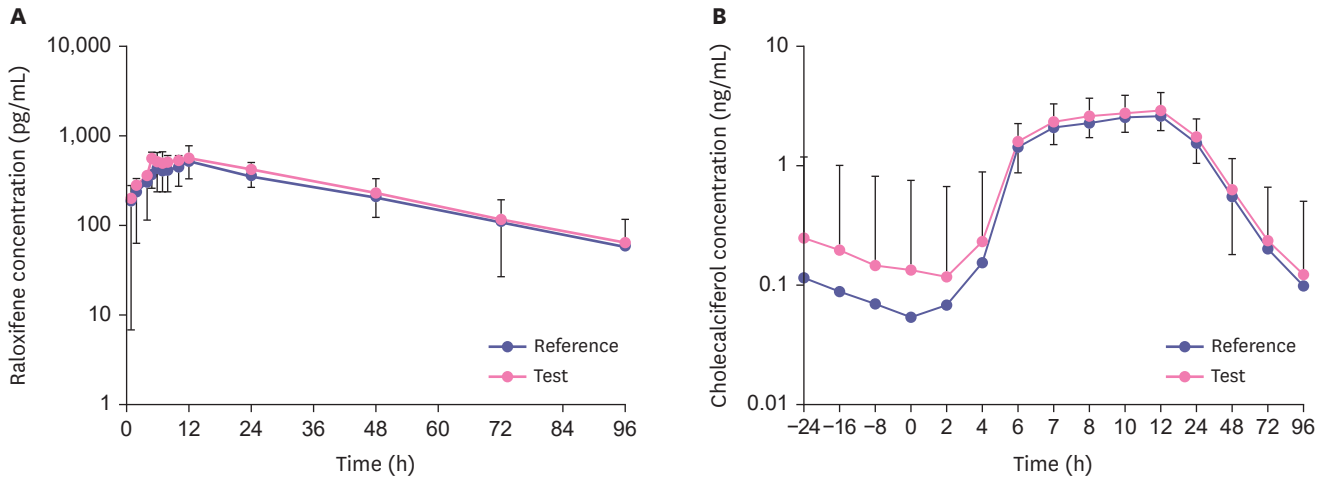

Figure 1. Mean plasma concentration-time profiles of raloxifene and cholecalciferol after administering a single oral dose of raloxifene 120 mg and cholecalciferol 1,600 IU as fixed dose combination or individual agents concomitantly. (A) Raloxifene (semilog scale); (B) Cholecalciferol, baseline-corrected (semilog scale). Error bars denote the standard deviations.

Table 3. Geometric mean ratios and 90% CIs for the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ following administration of raloxifene 120 mg and cholecalciferol 1,600 IU as a fixed-dose combination versus separate agents under fasted conditions in healthy male subjects (n = 46)

Variables	Geometric mean ratio (90% CI)	
	Raloxifene	Cholecalciferol, baseline-corrected
C_{max}	1.1010 (0.9945–1.2188)	1.0354 (0.9816–1.0921)
AUC_{0-t}	1.1364 (1.0584–1.2201)	1.0266 (0.9591–1.0989)
$AUC_{0-\infty}$	1.1641 (1.0611–1.2771)	1.0460 (0.9749–1.1223)

CI, confidence interval; C_{max}, maximum plasma concentration; AUC_{0-t}, area under the plasma concentration versus time curve from time 0 to the last quantifiable time point; $AUC_{0-\infty}$, area under the plasma concentration versus time curve from time 0 to infinity.

Safety and tolerability assessments

Single oral doses of raloxifene 120 mg and cholecalciferol 1,600 IU as the FDC tablets or as each components were generally well tolerated in this study. A total of three subjects (6.5%) of all 46 subjects who received at least one dose of the study drug reported 6 treatment-emergent AEs (TEAEs) during the study. Of the six TEAEs, one AE (hypercalciuria) was considered possibly related to the study drug. All AEs were mild in intensity and spontaneously resolved without specific treatment, and no serious AEs were reported.

DISCUSSION

The objective of the study was to compare the PKs and safety profiles, demonstrating the bioequivalence of an FDC (DP-R213) treatment (administration of two FDC tablets of raloxifene/cholecalciferol 60 mg/800 IU) and a separate agent treatment (concomitant administration of two tablets of raloxifene 60 mg and two tablets of cholecalciferol 800 IU) under fasting conditions in healthy subjects. AUC_{0-t} and C_{max} of raloxifene and cholecalciferol were comparable between FDC and the separate agents, leading to the 90% CIs for the GMRs for AUC_{0-t} and C_{max} falling entirely within the conventional bioequivalence range (0.8000–1.2500) between the two treatments.

https://doi.org/10.12793/tcp.2022.30.e13

As the daily recommended doses for raloxifene and cholecalciferol are 60 mg and 800 to 1000 IU for adults aged 50 and older, respectively, the FDC formulation containing raloxifene/cholecalciferol 60 mg/800 IU was developed. According to several reports, raloxifene 120 mg for 12–52 weeks was well tolerated [13,14]. FDC tablets of alendronate 70 mg plus cholecalciferol (either 2,800 or 5,600 IU) (Fosamax® Plus D) have been prescribed in a single, once-weekly dose [15]. Accordingly, the doses of raloxifene and cholecalciferol selected for this study (120 mg and 1,600 IU, respectively) were considered tolerable.

As cholecalciferol is endogenous, baseline correction was performed according to the exact method pre-specified in the study protocol [16]. After the arithmetic means of the plasma concentrations of cholecalciferol at −24, −16, −8, and 0 hours (pre-dose) were calculated to determine the individual endogenous pre-dose cholecalciferol concentration, baseline-corrected cholecalciferol concentrations were obtained by subtracting the mean pre-dose concentration from the post-dose concentrations for each subject. A negative plasma concentration produced from the baseline correction was set to 0 [16].

The intersubject variability %CV values of raloxifene $AUC_{0\text{-}t}$ and C_{max} for the FDC formulation in the study (32.2% and 44.7%, respectively) were comparable to the values for the separate agents in the present study (36.9% and 40.5%, respectively) and those that had been estimated from our earlier drug-drug interaction study (50.8% and 48.9%, respectively) [16]. However, the intersubject %CV values of raloxifene $AUC_{0\text{-}\infty}$ and $t_{1/2}$ for the FDC formulation (95.0% and 173.6%, respectively) in the present study were larger than those for the individual tablets from the current study (44.3% and 64.8%, respectively) and earlier PK studies (49.0% and 37.4%, respectively) [16]. As most regulatory agencies recommend the blood sampling to continue for at least three or more terminal elimination half-lives to cover at least 80% of $AUC_{0\text{-}\infty}$, the sampling schedule in the present study was planned to continue for 96 hours [17,18]. The mean ratio of $AUC_{0\text{-}t}$/ $AUC_{0\text{-}\infty}$ of raloxifene in the study was 89.6% for the FDC formulation and 89.7% for the separate agent, indicating that the sampling schedule predetermined in the study was adequate to provide a reliable estimate of exposure extent. However, the $AUC_{0\text{-}t}$/ $AUC_{0\text{-}\infty}$ ratio for the FDC formulation in four subjects was less than 80% (16.5–70%), leading to a large intersubject %CV for the $AUC_{0\text{-}\infty}$ and $t_{1/2}$ of raloxifene. One plausible factor responsible for the large intersubject %CV for the FDC formulation could be the formulation complexities. The aqueous solubility of raloxifene is poor [5]. Mitra et al. [19] reported that dissolution from the FDC formulation could slow down if high drug loading is required owing to restrictions on its final size [19].

Single doses of two tablets of raloxifene/cholecalciferol 60 mg/800 IU FDC formulation and co-administration of the separate raloxifene and cholecalciferol tablets were generally well tolerated in healthy adult subjects in the study. There were no serious AEs, and no subjects discontinued from the study because of an AE.

The subjects who participated in this study were all healthy and young. Therefore, further studies in postmenopausal osteoporosis patients might be beneficial for evaluating the safety and clinical efficacy of the newly developed FDC formulation, DP-R213.

In conclusion, raloxifene and cholecalciferol in the FDC formulation were determined to be bioequivalent to the corresponding separate agents. Furthermore, a single dose of raloxifene/cholecalciferol as the FDC or as single agents was well tolerated.

https://doi.org/10.12793/tcp.2022.30.e13

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