

# Comparison of *R*(+)- $\alpha$ -lipoic acid exposure after *R*(+)- $\alpha$ -lipoic acid 200 mg and 300 mg and thioctic acid 600 mg in healthy Korean male subjects

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Alpha-lipoic acid, a physiological form of thioctic acid, is a strong antioxidant that relieves diabetic neuropathic symptoms. *R*(+)- $\alpha$ -lipoic acid shows superior antioxidative effects to its racemate. We compared the pharmacokinetics (PKs) and tolerability of *R*(+)- and *S*(-)- $\alpha$ -lipoic acid after a single oral dose of *R*(+)- $\alpha$ -lipoic acid, Dexid<sup>®</sup>, and its racemate, thioctic acid in healthy male subjects. We used an open-label, randomized, single-dose, three-treatment, parallel study design to compare the PK exposure of the active form, *R*(+)- $\alpha$ -lipoic acid. Thirty subjects completed the study with no clinically relevant safety issues. The peak concentrations ( $C_{max}$ , mean $\pm$ SD) of *R*(+)- $\alpha$ -lipoic acid after doses of *R*(+)- $\alpha$ -lipoic acid 200 mg, 300 mg and thioctic acid 600 mg were 4186.8 $\pm$ 1956.7, 6985.6 $\pm$ 3775.8 and 6498.4 $\pm$ 3575.6  $\mu$ g/L, respectively, and the areas under the plasma concentration-time curve from 0 to the last measurable concentration ( $AUC_{last}$ ) were 1893.6 $\pm$ 759.4, 3575.2 $\pm$ 1149.2 and 3790.0 $\pm$ 1623.0  $\mu$ g $\cdot$ h<sup>-1</sup> $\cdot$ L<sup>-1</sup>, respectively. The geometric mean ratio and 90% confidence intervals of *R*(+)- $\alpha$ -lipoic acid 200 mg to thioctic acid 600 mg for the  $C_{max}$  and  $AUC_{last}$  were 0.71 (0.43–1.15) and 0.51 (0.37–0.70), respectively. The corresponding *R*(+)- $\alpha$ -lipoic acid 300 mg to thioctic acid 600 mg values were 1.11 (0.68–1.80) and 0.97 (0.71–1.34), respectively. In conclusion, *R*(+)- $\alpha$ -lipoic acid 300 mg showed PK characteristics similar to those of thioctic acid 600 mg and both formulations were well tolerated.

## Introduction

Patients with diabetes mellitus have the risk of developing microvascular complications such as retinopathy, nephropathy, and neuropathy.[1] At least one in every four patients with diabetes experiences distal symmetric neuropathy, which causes substantial morbidity and impairs the quality of life.[2] Free oxygen radicals may play an important role in the pathogenesis of diabetic neuropathy. The associated hyperglycemia induces overproduction of free oxygen radicals, which results in neuronal damage through imbalance in oxidative stress.[3,4]

Thioctic acid, which is a detoxification agent used for the treatment of diabetic polyneuropathy,[5] improves peripheral nerve function by reducing oxidative stress and increasing the glutathione content of the peripheral nerve.[4] The efficacy of thioctic acid has been clinically confirmed in previous clinical studies.[6] Thioctic acid is the racemic mixture of two optical isomers of  $\alpha$ -lipoic acid, *R*(+)- $\alpha$ -lipoic acid and *S*(-)- $\alpha$ -lipoic acid.[7] *R*(+)- $\alpha$ -lipoic acid is the naturally occurring form and is biologically active, whereas, *S*(-)- $\alpha$ -lipoic acid is a synthetic by-product during the production of  $\alpha$ -lipoic acid and antagonizes the action of *R*(+)- $\alpha$ -lipoic acid.[7]

The compound  $\alpha$ -lipoic acid is rapidly absorbed and eliminated after oral administration, with a median time to achieve maximum plasma concentration ( $t_{max}$ ) and mean plasma half-life of 15 min and 14 min (range, 10–20 min and 9–19 min), re-

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spectively.[7] It is extensively metabolized mainly by  $\beta$ -oxidation and S-methylation to dihydrolipoic acid, which can regenerate endogenous antioxidants.[8,9] The absolute bioavailability of racemic  $\alpha$ -lipoic acid is limited to approximately 30% owing to its high hepatic extraction, while the bioavailability of the  $R(+)$ - $\alpha$ -lipoic acid is higher than that of the  $S(-)$ - $\alpha$ -lipoic acid.[9]

The antioxidant effect of  $S(-)$ - $\alpha$ -lipoic acid is lower than that of  $R(+)$ - $\alpha$ -lipoic acid.[10] In addition,  $S(-)$ - $\alpha$ -lipoic acid inhibits the antioxidant activity of  $R(+)$ - $\alpha$ -lipoic acid and, therefore, a formulation containing  $R(+)$ - $\alpha$ -lipoic acid alone would be expected to be more beneficial than the racemic mixture of both forms.[10,11] In preclinical studies, the bioavailability of  $R(+)$ - $\alpha$ -lipoic was increased when  $R(+)$ - $\alpha$ -lipoic acid was administered alone compared to when it was administered as the racemic mixture.[12] The recommended dose of thioctic acid for diabetic neuropathy is 600 mg, which contains 300 mg each of  $R(+)$ - $\alpha$ -lipoic acid and  $S(-)$ - $\alpha$ -lipoic acid.[13] Based on the preclinical study results, it is expected that the pharmacokinetic (PK) characteristics of  $R(+)$ - $\alpha$ -lipoic acid after administration of thioctic acid 600 mg would be similar those obtained after the administration of  $R(+)$ - $\alpha$ -lipoic acid at 200 mg.[12] The present study aimed to compare the PK properties and tolerability of  $R(+)$ - and  $S(-)$ - $\alpha$ -lipoic acid after a single oral dose of  $R(+)$ - $\alpha$ -lipoic acid 200 mg and 300 mg with those of thioctic acid 600 mg in healthy, Korean male subjects.

## Methods

### Subjects

Healthy Korean male subjects (age 20–45 years, body weight 50–90 kg) were enrolled in the study. The subjects underwent screening examinations that included a medical history, physical examination, laboratory tests (hematology, clinical chemistry, and urinalysis), and measurement of vital signs (blood pressure and heart rate). Subjects who used any medication with the potential to affect the study results within 14 days before the start of the study; had a history of hypersensitivity to thioctic acid; had medically documented conditions including renal, hepatic, pulmonary, neurological, cardiovascular, gastrointestinal, endocrinological, psychiatric, oncological, and allergic disorders; had a history of myocardial infarction, hepatitis, or pancreatitis; and participated in another clinical trial within 3 months, were excluded. Written informed consent was obtained from all subjects prior to conducting any study-related procedures.

### Investigational product

The test formulation, Dexid® ( $R(+)$ - $\alpha$ -lipoic acid, tablet) and the reference formulation, thioctic acid (mixture of  $R(+)$ - and  $S(-)$ - $\alpha$ -lipoic acid, tablet) were manufactured by Bukwang Pharmaceutical Co. Ltd. (Seoul, Korea). Dexid® tablets, which contain only the  $R(+)$  form of  $\alpha$ -lipoic acid to avoid unnecessary intake of the antagonistic  $S(-)$  form. Dexid® 480 mg, the tromethamine salt and Dexid® 320 mg contain 300 mg and 200

mg  $R(+)$ - $\alpha$ -lipoic acid, respectively. Thioctic acid contains 300 mg  $R(+)$ - $\alpha$ -lipoic acid and 300 mg  $S(-)$ - $\alpha$ -lipoic acid.

### Study Design

The study had an open-label, randomized, single-dose, three-treatment, parallel design and was conducted at the Clinical Trials Center (CTC), Seoul National University Hospital (SNUH), Seoul, Korea. The protocol was approved by the Institutional Review Board at SNUH (ClinicalTrials.gov registry no.: NCT01258699). All study procedures were conducted in accordance with the principles of the Declaration of Helsinki and the Korean Good Clinical Practice. The subjects were randomly assigned to one of three treatment groups:  $R(+)$ - $\alpha$ -lipoic acid 200 mg or 300 mg or thioctic acid 600 mg.

After fasting for more than 10 h, the subjects were administered a single dose of the test drug along with 240 mL of water. Food and drink were prohibited for 4 h after dosing. Serial blood samples (7 mL) for the determination of plasma  $R(+)$ - $\alpha$ -lipoic acid and  $S(-)$ - $\alpha$ -lipoic acid concentrations were obtained pre-dose and at 0.08, 0.17, 0.25, 0.33, 0.5, 0.67, 1, 1.5, 2, 3, 4, 6, and 8 h post-dose. The samples were centrifuged at  $3,000 \times g$  for 10 min, and the separated plasma samples were stored at  $-70^{\circ}\text{C}$  until the analysis.

### Determination of plasma drug concentrations

The plasma  $R(+)$ - and  $S(-)$ - $\alpha$ -lipoic acid concentrations were determined by using a validated liquid chromatography (LC) system (Agilent 1100 series, Agilent Technologies, Santa Clara, CA) coupled with a tandem mass spectrometry system (API 4000 Quadrupole, AB Sciex, Framingham, MA) at the Department of Clinical Pharmacology and Therapeutics, SNUH (Seoul, Korea). To generate the standard curves, standard solutions of  $R(+)$ - and  $S(-)$ - $\alpha$ -lipoic acid were diluted in methanol to produce the calibration curve points equivalent to 5, 10, 30, 100, 300, 1000, 3000, and 5000 ng/mL. The standard calibration curves were constructed using the analyte/internal standard peak area ratios versus the nominal concentrations of the analytes.

The plasma samples (500  $\mu\text{L}$ ) were transferred into 15 mL tubes after vortexing. Then, ammonium acetate buffer (10 mM, 500  $\mu\text{L}$ ) and probenecid as the internal standard (10  $\mu\text{g}/\text{mL}$ , 100  $\mu\text{L}$ ) were added, and the mixtures were vortexed for 10 s, followed by the addition of ethyl acetate (4 mL) to each tube. Then, the samples were centrifuged at  $1,700 \times g$  for 10 min, and the supernatants were transferred into 5-mL glass tubes, followed by drying for 90 min using a speed vacuum. The residue was reconstituted in a solution of 1-propanol:distilled water (8:2, v/v; 100  $\mu\text{L}$ ). The high-performance liquid chromatography (HPLC) separation was performed by using a CHIRAL-AGP column (100  $\times$  4.0 mm, 5  $\mu\text{m}$ , ChromTech, Apple Valley, MA) at a flow rate of 0.5 mL/min.

The calibration curves were linear over the range of 5–5000 ng/mL for  $R(+)$ - $\alpha$ -lipoic acid and  $S(-)$ - $\alpha$ -lipoic acid ( $r \geq 0.9996$  and

$r \geq 0.9995$ , respectively). The lower limit of quantification was 5 ng/mL for both *R*(+)- and *S*(-)- $\alpha$ -lipoic acid. The accuracy was 88.8%–97.9% and 88.3%–98.4% for *R*(+)- and *S*(-)- $\alpha$ -lipoic acid, respectively. The precision coefficients of variation were  $\leq 5.0\%$  and  $\leq 4.1\%$  for *R*(+)- and *S*(-)- $\alpha$ -lipoic acid, respectively.

### Pharmacokinetic assessment

The individual pharmacokinetic parameters of *R*(+)- and *S*(-)- $\alpha$ -lipoic acid were calculated by a noncompartmental method, using the WinNonlin version 6.4 (Pharsight Corporation, Mountain View, CA). The peak concentration ( $C_{max}$ ) and time to achieve  $C_{max}$  ( $t_{max}$ ) were obtained by directly inspecting the individual plasma concentration-time profiles. The area under the plasma concentration-time curve from 0 to the last measurable concentration ( $AUC_{last}$ ) was calculated by the linear-up/log-down trapezoidal method. The terminal elimination constant ( $\lambda_z$ ) was estimated from the logarithm-transformed plasma concentration-time curve by linear regression, and the terminal half-life ( $t_{1/2}$ ) was calculated as  $\ln 2/\lambda_z$ . The AUC from 0 extrapolated to infinity ( $AUC_{0-\infty}$ ) was calculated as  $AUC_{last} + C_{last}/\lambda_z$ . The apparent clearance ( $CL/F$ ) was calculated as the administered dose divided by the  $AUC_{0-\infty}$ .

### Tolerability assessment

The tolerability was evaluated by physical examinations, measurement of vital signs (blood pressure and heart rate), 12-lead electrocardiograms (ECGs), clinical laboratory tests, and monitoring the adverse events (AEs) incidences. The AEs were monitored throughout the entire study period based on direct questioning and spontaneous reports and were recorded regardless of their suspected association with the study drugs. The re-

lationship of the AEs to the study medications was subsequently assessed and classified by the investigators.

### Statistical analysis

The demographics, tolerability data, and pharmacokinetic parameters were summarized by using descriptive statistics. The geometric mean ratio (GMR) and associated 90% confidence intervals (CIs) of *R*(+)- $\alpha$ -lipoic acid 200 mg versus thioctic acid 600 mg and *R*(+)- $\alpha$ -lipoic acid 300 mg versus thioctic acid 600 mg were calculated for the log-transformed  $C_{max}$  and  $AUC_{last}$  to compare the PK parameters between treatments. The statistical analysis was performed by using the statistical analysis software (SAS) version 9.4 program (SAS Institute, Cary, NC).

## Results

### Subjects

Thirty-three healthy Korean male subjects were enrolled, and three were dropped due to consent withdrawal, abnormality in baseline laboratory test, and 30 completed the study (Fig. 1). The mean  $\pm$  SD of the age, height, and weight of these subjects were  $24.6 \pm 4.2$  years,  $173.7 \pm 5.5$  cm, and  $67.1 \pm 7.1$  kg, respectively. There were no significant differences in the demographic characteristics between the three treatment groups (Table 1).

### Pharmacokinetics

The mean plasma *R*(+)- $\alpha$ -lipoic concentration-time curves after a single, oral dose of *R*(+)- $\alpha$ -lipoic acid 200 mg or 300 mg and thioctic acid 600 mg are illustrated in Figure 2. The distribution of the individual  $C_{max}$  and  $AUC_{last}$  of *R*(+)- $\alpha$ -lipoic are illustrated in Figure 3. Based on the results of PK profiles,

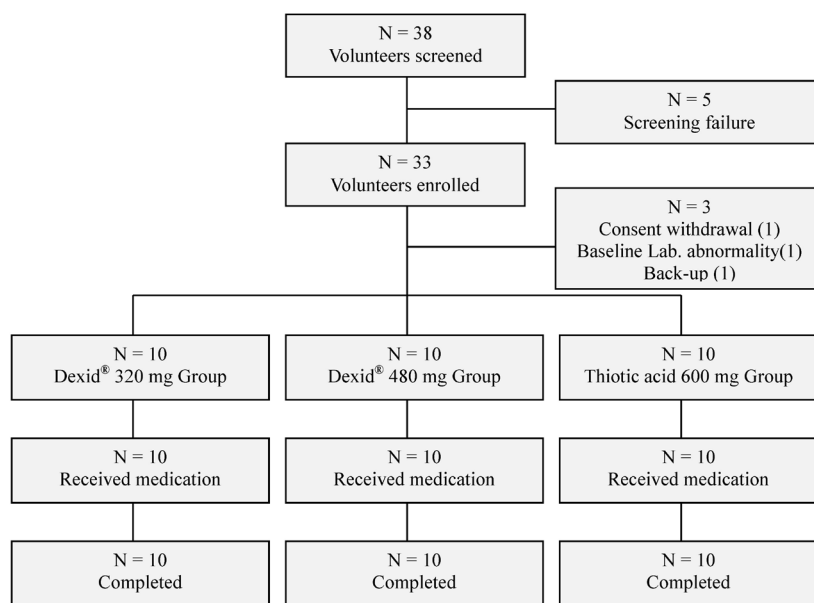
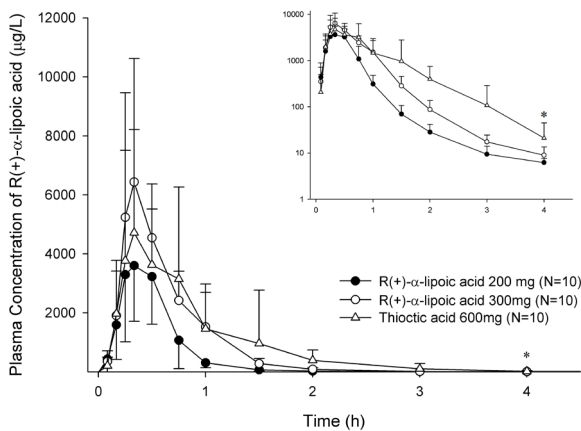


Figure 1. Disposition of the study subjects.

**Table 1.** Demographic characteristics of the study subjects

	Treatment			Total (N=30)	p-value <sup>1)</sup>
	R(+)-α-lipoic acid 200 mg (Dexid® 320 mg) (N=10)	R(+)-α-lipoic acid 300 mg (Dexid® 480 mg) (N=10)	Thioctic acid 600 mg (N=10)		
Age (years)	25.3±4.9	25.2±5.2	23.2±1.8	24.6±4.2	0.78
Height (cm)	174.6±4.5	172.0±6.5	174.5±5.6	173.7±5.5	0.58
Weight (kg)	68.0±6.3	64.5±9.3	68.8±5.1	67.1±7.1	0.17

\*Values are presented as mean±SD, <sup>1)</sup>Kruskal-Wallis test.

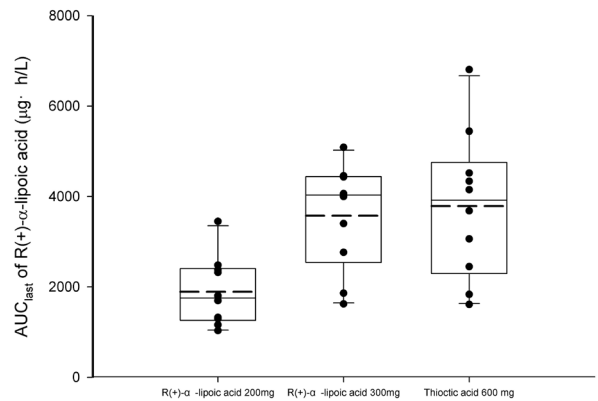
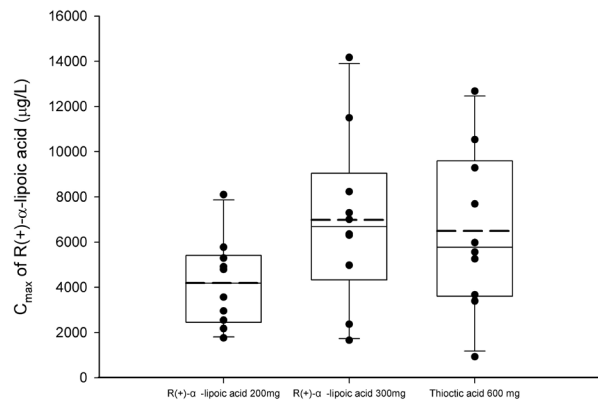


**Figure 2.** Mean plasma concentration-time profiles of R(+)-α-lipoic acid after a single oral administration of R(+)-α-lipoic acid 200 mg or 300 mg or thioctic acid 600 mg. Inset shows profile by log-linear scale. Bars represent SD. (\* N=2 for R(+)-α-lipoic acid 200 mg, N=7 for R(+)-α-lipoic acid 300 mg and thioctic acid 600 mg)

the PK characteristics after a single, oral dose of R(+)-α-lipoic acid 300 mg was similar to those after a single, oral dose of thioctic acid 600 mg. The  $t_{max}$  and  $t_{1/2}$  were similar among the three treatment groups. The  $C_{max}$  for R(+)-α-lipoic acid 200 mg and 300 mg and thioctic acid 600 mg was  $4186.8 \pm 1956.7$ ,  $6985.6 \pm 3775.8$ , and  $6498.4 \pm 3575.6$  µg/L, respectively, and the  $AUC_{last}$  was  $1893.6 \pm 759.4$ ,  $3575.2 \pm 1149.2$  and  $3790.0 \pm 1623.0$  µg·h<sup>-1</sup>·L<sup>-1</sup>, respectively (Table 2). To compare the PK characteristics among the three treatment groups, evaluation and comparison of PK parameters of each group was done. The GMR and associated 90% CIs of R(+)-α-lipoic acid 200 mg to thioctic acid 600 mg for the  $C_{max}$  and  $AUC_{last}$  were 0.71 (0.43–1.15) and 0.51 (0.37–0.70), respectively. The corresponding values for R(+)-α-lipoic acid 300 mg to thioctic acid 600 mg were 1.11 (0.68–1.80) and 0.97 (0.71–1.34), respectively (Table 3).

**Tolerability**

No serious AEs were reported, and no subjects discontinued the study because of AEs. One subject who received the thioctic acid 600 mg reported moderate urticaria, which was relieved after the administration of chlorpheniramine and ranitidine. The



**Figure 3.** Comparison of peak concentration ( $C_{max}$ , upper) and area under the plasma concentration-time curve from 0 to the last measurable concentration ( $AUC_{last}$ , lower) of R(+)-α-lipoic acid after a single oral administration of R(+)-α-lipoic acid 200 mg or 300 mg or thioctic acid 600 mg. Boxes indicate interquartile range and whisker bars indicate 10th and 90th percentiles. Horizontal bars locate in the middle of the boxes represent median and the long-dashed line shows mean.

AE was considered possibly related to the study drug. No clinically significant changes were noted in the vital signs, physical examinations, ECGs, or clinical laboratory results throughout the study period.

**Table 2.** Summary of Pharmacokinetic Parameters of *R*(+)- $\alpha$ -lipoic acid and *S*(-)- $\alpha$ -lipoic acid after a single oral administration of *R*(+)- $\alpha$ -lipoic acid 200 mg, 300 mg or thioctic acid 600 mg

Parameters*		<i>R</i> (+)- $\alpha$ -lipoic acid 200 mg (Dexid® 320 mg) (N=10)		<i>R</i> (+)- $\alpha$ -lipoic acid 300 mg (Dexid® 480 mg) (N=10)		Thioctic acid 600 mg (N=10)	
		<i>R</i> (+)- $\alpha$ -lipoic acid	<i>S</i> (-)- $\alpha$ -lipoic acid	<i>R</i> (+)- $\alpha$ -lipoic acid	<i>S</i> (-)- $\alpha$ -lipoic acid	<i>R</i> (+)- $\alpha$ -lipoic acid	<i>S</i> (-)- $\alpha$ -lipoic acid
$t_{max}$ (h)	Median	0.33	-	0.33	-	0.33	0.33
	Range	(0.25-0.75)		(0.25-1.00)		(0.25-0.75)	(0.25-0.75)
$C_{max}$ ( $\mu$ g/L)	Mean $\pm$ SD	4186.8 $\pm$ 1956.7	-	6985.6 $\pm$ 3775.8	-	6498.4 $\pm$ 3575.6	3552.6 $\pm$ 1942.4
	Range	(1761.0-8099.0)		(1655.0-14170.0)		(930.1-12680.0)	(532.8-2908.2)
$AUC_{last}$ ( $\mu$ g·h/L)	Mean $\pm$ SD	1893.6 $\pm$ 759.4	-	3575.2 $\pm$ 1149.2	-	3790.0 $\pm$ 1623.0	1969.4 $\pm$ 1031.5
	Range	(1031.2-3448.0)		(1622.7-5085.3)		(1610.4-6807.3)	(812.3-3770.5)
$AUC_{0-\infty}$ ( $\mu$ g·h/L)	Mean $\pm$ SD	1900.7 $\pm$ 758.9	-	3585.5 $\pm$ 1146.0	-	3805.0 $\pm$ 1623.7	2073.6 $\pm$ 951.8
	Range	(1038.6-3454.0)		(1627.8-5091.9)		(1621.3-6833.4)	(851.5-3777.9)
$t_{1/2}$ (h)	Mean $\pm$ SD	0.7 $\pm$ 0.2	-	0.7 $\pm$ 0.3	-	0.6 $\pm$ 0.2	0.9 $\pm$ 1.4
	Range	(0.5-1.1)		(0.4-1.2)		(0.3-0.9)	(0.3-4.8)
CL/F (L/h)	Mean $\pm$ SD	120.4 $\pm$ 44.6	-	95.5 $\pm$ 42.6	-	95.3 $\pm$ 46.9	175.5 $\pm$ 83.3
	Range	(57.9-192.6)		(58.9-184.3)		(43.9-185.0)	(79.4-352.3)

\* $C_{max}$ : the peak plasma concentration,  $t_{max}$ : time to maximum plasma concentration,  $AUC_{last}$ : the area under the plasma concentration versus time curve from 0 to the last measurable concentration,  $AUC_{0-\infty}$ : the area under the plasma concentration versus time curve from 0 extrapolated to infinity,  $t_{1/2}$ : terminal half-life, CL/F: apparent clearance.

**Table 3.** Comparison of pharmacokinetic parameters after a single oral administration of *R*(+)- $\alpha$ -lipoic acid 200 mg, 300 mg or thioctic acid 600 mg

Parameters	Geometric mean			Geometric Mean Ratio (90% Confidence Interval)	
	<i>R</i> (+)- $\alpha$ -lipoic acid 200 mg (Dexid® 320 mg) (N=10)	<i>R</i> (+)- $\alpha$ -lipoic acid 300 mg (Dexid® 480 mg) (N=10)	Thioctic acid 600 mg (N=10)	<i>R</i> (+)- $\alpha$ -lipoic acid 200 mg / Thioctic acid 600 mg	<i>R</i> (+)- $\alpha$ -lipoic acid 300 mg / Thioctic acid 600 mg
$C_{max}$ ( $\mu$ g/L)	3781.7	5926.9	5353.0	0.71 (0.43-1.15)	1.11 (0.68-1.80)
$AUC_{last}$ ( $\mu$ g·h/L)	1766.6	3369.1	3460.6	0.51 (0.37-0.70)	0.97 (0.71-1.34)
$AUC_{0-\infty}$ ( $\mu$ g·h/L)	1774.2	3381.7	3477.0	0.51 (0.37-0.70)	0.97 (0.71-1.33)

\* $C_{max}$ : the peak concentration,  $AUC_{last}$ : the area under the plasma concentration versus time curve from 0 to the last measurable concentration,  $AUC_{0-\infty}$ : the area under the plasma concentration versus time curve from 0 extrapolated to infinity.

## Discussion

Although the chemical composition of the investigational products that were used in this study were not the same, the point estimate of the GMR of the test (Dexid® 480 mg) to the reference was close to 1.00 for both the  $C_{max}$  and  $AUC_{last}$ . Furthermore, PK parameters including  $t_{max}$ ,  $t_{1/2}$  and CL/F were also similar to each other. This results implies that the PK characteristics of *R*(+)- $\alpha$ -lipoic acid after a single, oral dose of *R*(+)- $\alpha$ -lipoic acid 300 mg was similar to those after a single, oral dose of thioctic acid 600 mg.

The designs of comparative PK study include parallel design,

cross-over design etc. The selection of the design is based on half-life of the drug, inter-individual variability and intra-individual variability, the risk for multiple exposure to the drug, and the urgency of the study. In this study, the parallel design was adopted due to the need to complete the study within a limited timeline. If the cross-over design has been employed, similarity of PK profiles could have been tested with a smaller number of subjects.

The PK characteristics of the enantiomer of a stereoisomeric drug can be changed when the drug is administered as a racemic mixture due to the enantiomer-enantiomer interaction.

For example, the clearance of (S)-propafenone is reduced by half when it is administered as the racemate form compared with when it is administered as the (S)-propafenone form.[14] In a previous *in vivo* study, the salt form of R(+)- $\alpha$ -lipoic acid was considerably more bioavailable than an equivalent dose of the racemate. This indicated that the S(-)- $\alpha$ -lipoic acid in the racemate formulation may function as a competitive inhibitor of the absorption of R(+)- $\alpha$ -lipoic acid.[7] There is a possibility that the absorption of R(+)- $\alpha$ -lipoic acid can be improved in the absence of S(-)- $\alpha$ -lipoic acid. Therefore, in this study, the R(+)- $\alpha$ -lipoic acid 200 mg and 300 mg were compared with thioctic acid, which contains 300 mg of R(+)- $\alpha$ -lipoic acid. However, the R(+)- $\alpha$ -lipoic acid 300 mg but not 200 mg showed similar PK characteristics with thioctic acid 600 mg, which indicates that the S(-)- $\alpha$ -lipoic acid did not alter the systemic absorption of R(+)- $\alpha$ -lipoic acid. These results confirm that the PK properties of the racemate can vary according to the animal species and, therefore, the assessment of the PK characteristics in humans is essential when the chemical composition is changed even if animal data exists.

In the case of the racemate compound, the interconversion of R(+)- and S(-)-isomers can occur. For example, thalidomide is a former racemic sedative of R(+)- and S(-)-isomers and both enantiomers of thalidomide exhibit interconversion *in vivo*. [15] Since the interconversion of R(+)- and S(-)- $\alpha$ -lipoic acid *in vivo* is possible, the plasma concentrations of both forms were determined at all time points to identify if this conversion occurred this study. Following the administration of R(+)- $\alpha$ -lipoic acid 200 mg and 300 mg, no measurable S(-)- $\alpha$ -lipoic acid was detected in the plasma at all time points after the administration of R(+)- $\alpha$ -lipoic acid, which showed there was no enantiomeric interconversion between the R(+)- and S(-)- $\alpha$ -lipoic forms in humans. The individual absorption and elimination of  $\alpha$ -lipoic acid after oral administration varied between individuals and some showed a double peak phenomenon. Considering the low interindividual PK variability after intravenous administration in a previous study, the individual variability of the first pass metabolism may contribute to this phenomenon.

In conclusion, The R(+)- $\alpha$ -lipoic acid 300 mg showed PK characteristics similar to those of thioctic acid 600 mg, based on the PK and statistical analyses in this study, and the R(+)- $\alpha$ -lipoic acid at doses of 200 mg and 300 mg formulations were well tolerated. The R(+)- $\alpha$ -lipoic acid 300 mg formulation can be an alternative treatment of thioctic acid 600 mg and the development of R(+)-form drug without its stereoisomer, S(-) form, is beneficial to patients. The development strategy for a racemate drug using in this drug can be applied to other stereoisomeric drugs.

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## Conflict of interest

The sponsors of this study, Bukwang Pharmaceutical Co., Ltd., Seoul, Republic of Korea, had a minor role in the study design and review of the manuscript. Kwang-Ok Lee is an employee of Bukwang Pharm. Co., Ltd., Korea. All the other authors declare no other conflicts of interest with regard to the content of this article.

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