Single-dose Intravenous Safety, Tolerability, and Pharmacokinetics and Absolute Bioavailability of LCB01-0371

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ABSTRACT

Purpose: LCB01-0371 is a novel broad-spectrum oxazolidinone antibacterial agent under investigation for the treatment of infection by gram-positive pathogens, including methicillin-resistant *Staphylo-coccus aureus*. This study evaluated the safety, tolerability, and pharmacokinetics of LCB01-0371 after a single intravenous (IV) infusion and determined its absolute oral bioavailability at a therapeutic dose of 800 mg.

Methods: : This study was conducted in 2 parts. The first part was a single-blind, placebo-controlled, escalating single IV dose study (200, 400, 800, and 1200 mg) of LCB01-0371 via 2 different infusion regimens (250 mL over 60 min or 150 mL over 30 min) in 36 healthy male volunteers. The second part was an open-label, 2-way crossover design study in which 8 subjects were randomly assigned to 1 of 2 sequences of a single oral (800 mg) or IV (400 mg) administration of LCB01-0371. Safety assessments were conducted at regular intervals. Blood and urine were serially sampled, and drug concentrations were measured for up to 24 h to calculate pharmacokinetic parameters.

Findings: LCB01-0371 after IV administration was generally safe and well tolerated up to 800 mg regardless of the infusion regimen. Adverse events were mild, excluding nausea at the highest dose, and resolved spontaneously. After a single IV administration, LCB01-0371 exhibited linear pharmacokinetic properties over the range of 200−800 mg. The elimination $t_{1/2}$, volume of distribution, and clearance ranged from 1.48 to 1.68 h, 57.74−76.72 L, and 33.17−43.31 L/h, respectively, and they remained unchanged over the corresponding dose range. C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ increased in a dose-dependent manner. The dose-normalized total exposure after single PO and IV dosing were equivalent, with 90% CIs of the geometric least squares mean ratio of 86.6%−110% for AUC_{0-last} and 86.6%−111% for $AUC_{0-\infty}$. The dose-normalized C_{max} was not equivalent between oral and IV dosing, with a 90% CI of the geometric least squares mean ratio of 50.0%−105%. The absolute oral bioavailability of LCB01-0371 after a single 800-mg dose was 99.75%.

Implications: After a single IV administration, LCB01-0371 was well tolerated in healthy volunteers at doses up to 800 mg, and it exhibited linear pharmacokinetic properties. The comparable total systemic exposure between IV and oral administration supports the ability to switch administration routes without a need for dose adjustment. ClinicalTrials.gov identifier: NCT02882789. (*Clin Ther*. 2019;41:92−106)

Key Words: bioavailability, intravenous, LCB01-0371, pharmacokinetics, safety, tolerability.

INTRODUCTION

The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections has been increasing globally, especially in Asia.[1−4] Furthermore, this infection often results in bacteremia and septic shock.[5,6] Due to this clinical course, the development

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of antibiotic agents against both hospital- and community-associated MRSA is strongly required.[7]

Vancomycin has been a treatment of choice for MRSA infection, but the development of strains with reduced sensitivity and access via only the parenteral route has compromised its clinical use.[8,9] Oxazolidinones represent a new class of antibiotics that inhibit the growth of gram-positive pathogens, including MRSA, by blocking microbial mRNA translation.[10] Linezolid was the first oxazolidinone antibiotic approved in the United States and many countries worldwide. Despite its wide success, linezolid's use has been limited by the emergence of bacterial resistance and the potential for adverse events (AEs), especially hematologic abnormalities, over a prolonged course of therapy.[11–15] Thus, there is an unmet need for newer oxazolidinones with broad-spectrum activity and lower risks of use-limiting AEs.

LCB01-0371 is an investigational oxazolidinone with a cyclic amidrazone group that is currently in Phase II development. LCB01-0371 exhibited potent broad-spectrum antibacterial activity both in vitro and in vivo against gram-positive clinical isolates containing MRSA.[16] In a multiple ascending dose study, LCB01-0371 exerted early serum inhibitory and bactericidal activities ex vivo against 4 tested strains (*S aureus* ATCC29213, *Enterococcus faecalis* ATCC51299, MRSA ATCC43300, and Streptococcus pneumoniae ATCC49619).

Although oxazolidinones have been generally well tolerated, one concern with this drug class is reversible myelosuppression, especially thrombocytopenia.[15] This finding is well documented with linezolid, primarily for treatment courses >14 days.[11,17–19] In preclinical repeated dose toxicology studies, LCB01-0371 was expected to be safer than linezolid (unpublished data). Furthermore, in a recently published Phase I study, oral administration of LCB01-0371 at doses ranging from 800 mg once daily to 1200 mg BID for 21 days had no significant effect on any hematologic values.[20] After repeated oral administration, LCB01-0371 is absorbed rapidly within 2 h, and its accumulation on day 7 ranged from 1.10- to 1.46-fold. The elimination $t_{1/2}$ was 1.64–1.94 h, which remained unchanged across doses of 400–1600 mg. For patients with comorbidities or signs of moderate or severe disease, conventional treatment of intravenous (IV) antibiotics is initially used. The capability to simply switch antibacterial agent from IV to PO dosing after the patient's clinical improvement can cut down on the durations of catheterization and hospital stay.

The present study assessed the safety, tolerability, and pharmacokinetic variables of LCB01-0371 after a single IV administration and investigated the absolute oral bioavailability of LCB01-0371 at a therapeutic dose of 800 mg, which should clarify the appropriateness of switching between IV and PO formulations.

Subjects and Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and is registered with ClinicalTrials.gov (NCT02882789). Our local institutional review board (Asan Medical Center Institutional Review Board, No. 2013-0088) and the Ministry of Food and Drug Safety of Korea (Investigational New Drug Application No. 11870) approved the present study protocol, and written informed consent was obtained from each subject before screening. In addition, the written informed consent for another study using samples derived from subjects in this study (informed consent for the research use of human biological materials) was obtained from each subject. The additional study was "In vitro and in vivo comparative metabolism of LCB01-0371 in rat, dog, and human" performed in the Department of Pharmacology, Inje University College of Medicine (Busan, South Korea) (unpublished data).

Subjects

Male subjects aged between 19 and 40 years who were in good health based on physical examination, medical history, concomitant drug use, 12-lead ECG profiles, and clinical laboratory test results were eligible. Subjects were excluded if they had any evidence of diseases of the major organs; hepatitis B or C virus, HIV, or syphilis infection; prolonged QTc intervals on ECG; or any clinically significant hematology, chemistry, or urinalysis data abnormalities.

Study Design

This study was conducted in 2 parts. As shown in Figure 1, the first part was a single-blind, placebo-controlled, single ascending dose study with IV administration of LCB01-0371; the second part was

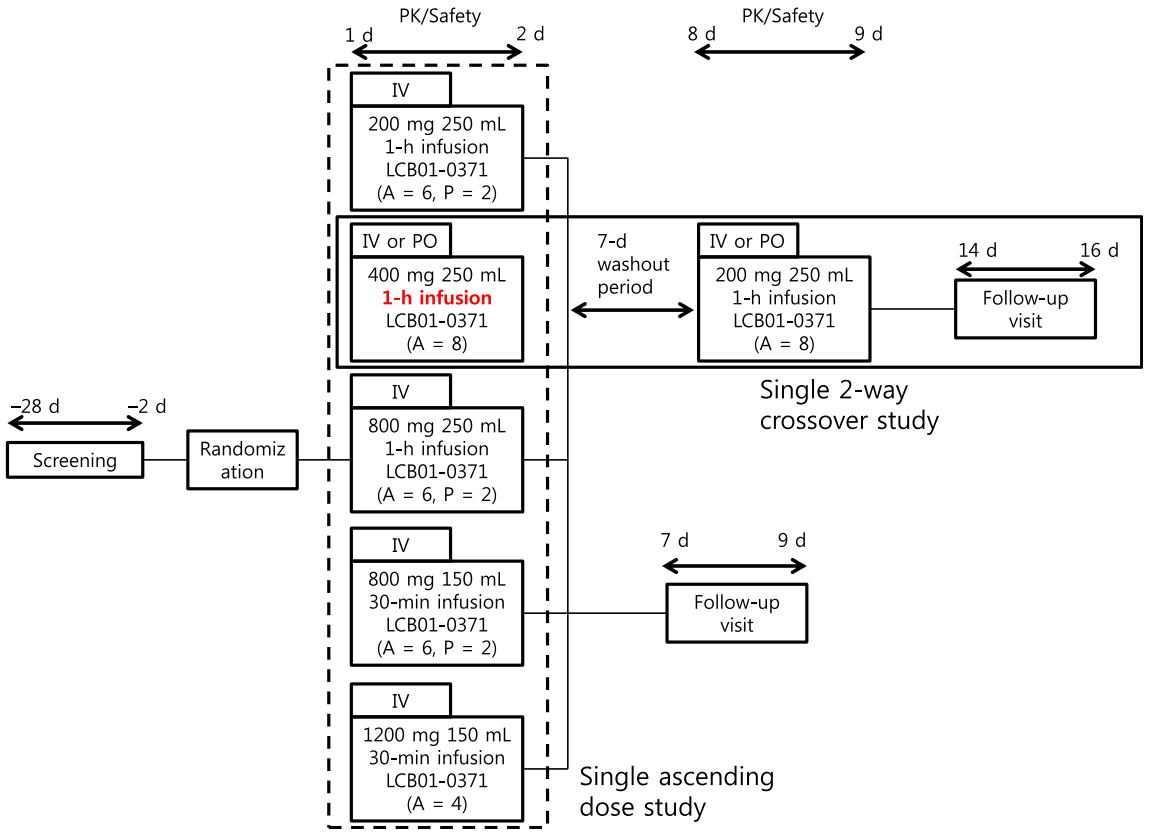

Figure 1. Study design. A = number of subjects administered LCB01-0371; P = number of subjects receiving placebo; IV = intravenous; PK = pharmacokinetics.

a single-dose, open-label, 2-way crossover design study featuring IV or PO administration of LCB01-0371. In the single escalating dose study, a single IV dose of 200, 400, 800, or 1200 mg of LCB01-0371 was administered via 2 different infusion regimens (250 mL over 60 min or 150 mL over 30 min) to 36 healthy male volunteers, and the safety, tolerability, and pharmacokinetic variables were assessed. In total, 24 subjects received a single 60-min IV infusion of 200, 400, or 800 mg of LCB01-0371 or placebo, and 12 subjects received a single 30-min IV infusion of 800 or 1200 mg of LCB01-0371 or placebo. The 800-mg dose groups including both infusion regimens, and the 1200-mg dose group was scheduled to be divided into 2 subgroups of 4 subjects each. The decision to proceed to the next dose level was made via a safety review meeting based on the safety profile, tolerability, and available pharmacokinetic data of the preceding dose. In the 400-mg administration group, 8 subjects were randomly assigned to IV dosing followed by PO dosing of 800 mg of LCB01-0371, or vice versa, separated by a 7-day washout period, and absolute bioavailability was evaluated. The subjects were observed at the study site from day −1 to day 2 and followed up for 7–9 days. Food intake was prohibited for >10 h before drug administration and 4 h after drug administration.

Study Drug and Procedures

LCB01-0371 and placebo for IV administration were supplied by the sponsor in a lyophilized powder (100-mg vial) and 5% dextrose in water, respectively. LCB01-0371 for PO administration was also provided by the sponsor in a 400-mg tablet. PO LCB01-0371 administration was performed with

150 mL of water, and IV LCB01-0371 was administered in 5% dextrose in water. Indwelling catheters were inserted for all enrolled subjects for IV infusions.

Safety Evaluation

All subjects who received at least 1 dose of the study treatment were included in the safety analysis. The assessment of vital signs, physical examination, AE monitoring, clinical laboratory tests including clinical chemistry, hematology, blood coagulation testing, urinalysis, and 12-lead ECG studies were performed according to predefined schedules. In addition, local tolerability at the infusion site and its associated area was evaluated by using modified Visual Infusion Phlebitis (VIP) scoring criteria.[21] The VIP score was recorded before, immediately after, and 4, 6, and 24 h after the end of the infusion. If the VIP score is ≥ 1, the findings are reported as AEs, followed up, assessed, and recorded until the score falls within the clinically meaningless range or a satisfactory explanation of the change is provided. Subjects were monitored carefully throughout each dosing period for AEs. The relationship of AEs to the study drug, their severity, and the clinical significance of safety parameters were evaluated by the study investigator.

Sample Collection

Blood samples (~8 mL) were collected before, during, and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, and 24 h after dosing in the 250-mL IV group. For the 150-mL IV group, blood samples were collected before, during, and 0.08, 0.16, 0.33, 0.5, 0.66, 0.83, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h after dosing. Blood samples after PO administration were collected before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 24 h after dosing. Blood samples taken at each time point were collected into vials containing heparin as an anticoagulant and centrifuged to obtain plasma samples. About 3−4 mL of plasma was obtained from a total of 8 mL of blood (<0.5 fraction of blood). The plasma samples were divided into 3 tubes in 0.8-mL increments. One sample (the primary sample) was used for concentration measurement, the second sample was stored for back-up, and the third sample was sent to another laboratory for further study such as metabolite profiling. The re-measurement that is performed as needed was also planned to be done using the primary sample. Urine samples were collected over the intervals of 0−4, 4 to 8, 8 to 12, and 12−24 h for the first part of the study. Blood and urine samples were stored at −70 °C until subsequent analysis.

Analytical Methods

To validate the method of LCB01-0371 determination in human plasma, LCB01-0371 and its internal standard provided by LegoChem Biosciences, Inc (LCB01-0720) were extracted with acetonitrile. The concentrations of the prepared samples were determined by using HPLC-MS/MS. The method was validated over an LCB01-0371 concentration range of 5.0−20,000 ng/mL, and a 0.1-mL aliquot was used for analysis. The intra-assay data of quality control samples in the concentration range of 15−16,000 ng/mL were determined with a precision of 1.5%−5.9% and an accuracy of 92.6%−109.3%. The interassay data of quality control samples in the same concentration range were determined with a precision of 2.5%−5.2% and an accuracy of 93.5%−107.1%. The interassay data of back-calculated concentrations in the calibrator were determined with a precision of 2.2%−6.3% and an accuracy of 94.7%−103.3%. When the concentration of the analyte exceeded the upper limit of the calibration curve (20,000 ng/mL), it was diluted to the appropriate concentration with the same type of blank plasma. Assessment of the dilution effect of quality-control samples was performed at 2 concentrations (30 and 32,000 ng/mL) with dilution factor 2, and the precision (4.8% and 2.0%) and accuracy (102.5% and 100.6%) were evaluated by repeating testing 5 times for each concentration.

To validate the method of LCB01-0371 determination in human urine, LCB01-0371 and its internal standard were extracted with acetonitrile. The concentrations of prepared samples were determined by using HPLC-MS/MS. The method was validated over an LCB01-0371 concentration range of 5.0−20,000 ng/mL, and a 0.1-mL aliquot was used for analysis. The intra-assay data of quality control samples of the concentration range of 150 to 16,000 ng/mL were determined with a precision of 1.7%−8.8% and an accuracy of 96.4%−106.6%. The interassay data of quality control samples over the same concentration range were determined with a

precision of 2.5%−5.2% and an accuracy of 93.5%−107.1%. The interassay data of back-calculated concentrations in the calibrator were determined with a precision of 2.4%−7.9% and an accuracy of 97.1%−105.1%. When the concentration of the analyte exceeded the upper limit of the calibration curve (20,000 ng/mL), it was diluted to the appropriate concentration with the same type of blank urine. Assessment of the dilution effect of quality-control samples was performed at 3 concentrations (20,000, 60,000, and 200,000 ng/mL for 10-fold dilution; and 600, 40,000, and 640,000 ng/mL for 40-fold dilution) for each dilution factor 10 and 40, and the precision (1.4%−6.4% for 10-fold dilution, 4.0%−5.5% for 40-fold dilution) and accuracy (98.2%−106.3% for 10-fold dilution, 97.5%−109.0% for 40- fold dilution) were evaluated by repeating testing 5 times for each concentration.

Pharmacokinetic Analysis

LCB01-0371 pharmacokinetic variables in plasma were analyzed by using noncompartmental methods with the NonCompart package in R statistical software version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). C_{max} and T_{max} were estimated by visually inspecting the plasma concentration versus time data; $t_{1/2}$ was calculated as ln (2)/k_e, where k_e is the elimination rate constant determined from the slope of the linear regression analysis of the apparent terminal linear portion of the log concentration time curve using a minimum of the last 3 data points. AUC_{0-last} was computed by using the linear trapezoidal method. $AUC_{0-\infty}$ was calculated as the sum of AUC_{0-last} and C_{last}/k_e, where C_{last} is the last measurable drug concentration. Clearance (CL) was calculated by dividing the administered dose by $AUC_{0-\infty}$. The volume of distribution in the terminal phase ($V_{d,z}$) was obtained by using the formula CL/k_e; the volume of distribution at steady state ($V_{d,ss}$) was obtained by the product of mean residence time and CL. The amount of unchanged LCB01-0371 in urine after 24 h (A_e) was determined from the cumulative amount excreted in urine. The fraction of dose recovery unchanged in urine (f_e) was expressed as a percentage of the administered dose. Renal clearance (CL_R) was calculated as A_e divided by AUC_{0-last}.

The dose proportionality of C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ according to dose group was assessed by using a power model. The linear relationship between log-transformed pharmacokinetic parameters and the natural log of the dose was tested. A point estimate and its 90% CI were produced for the population mean slope of each pharmacokinetic parameter.

To determine the absolute bioavailability of PO LCB01-0371 800 mg PO, an ANOVA was performed. The ANOVA model involved ln-transformed C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ as the dependent variables; treatment effects, study period, and sequence as fixed effects; and a random subject (sequence) effect. The point estimates (geometric least squares mean) and 90% CIs for the ratio between PO and IV LCB01-0371 for pharmacokinetic parameters were computed by taking re-transformation of logarithmic data. The statistical assessment was performed by using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Study Population

In total, 36 subjects were enrolled, 30 of whom received IV LCB01-0371 only or both IV and PO LCB01-0371, with 6 receiving placebo. Thirty-four subjects completed all assessments. In the single ascending dose study, 2 of 4 subjects who received the active drug in the first subgroup of the 1200-mg dose group discontinued treatment due to moderate AEs. Based on the study discontinuation criteria in which the percentage of dropouts among subjects who were administered the active drug could not exceed 30%, the study was stopped, and the second subgroup could not be recruited. All 8 subjects targeted for the absolute bioavailability assessment completed the study.

The mean participant age was 26.53 years (range, 19−39 years). The average body weight and height of the participants were 71.86 kg (range, 55.25−89.25 kg) and 173.67 cm (range, 162.4−186.3 cm), respectively, and the mean body mass index was 23.79 kg/m^2 (range, 20−27.6 kg/m^2).

Safety and Tolerability

No serious and severe AEs related to LCB01-0371 were observed in this study. Table I summarizes all AEs and their causalities in the treatment group. In total, 15 AEs were reported by 11 (30.56%) subjects; whereas 14 AEs were reported by 10 (33.33%) of the 30 subjects who received the active

Table I. Summary of adverse events and their causal relationships after LCB01-0371 administration.

Variable	Dose/Route, Infusion Duration								
	Placebo	200 mg/IV, 60 min	400 mg/IV, 60 min	800 mg/PO	800 mg/IV, 60 min		800 mg/IV, 30 min		1200 mg/IV, 30 min
	(n = 6)	(n = 6)	(n = 8)	(n = 8)	(n = 6)		(n = 6)		(n = 4)
Relationship to study drug	Definitely not	Unlikely	Possible	—	Unlikely	Probable	Definitely not	Unlikely	Probable
Adverse event									
Acne, forehead	0	1	0	0	0	0	0	0	0
Forearm bruise, left	1	0	0	0	0	0	0	0	0
Infusion site pain, right arm	0	0	0	0	0	0	0	0	1
Infusion site paraesthesia, right arm	0	0	0	0	0	0	0	0	2
Infusion site paraesthesia, right lower arm	0	0	1	0	0	0	0	0	0
Infusion site phlebitis, left arm	0	1	0	0	0	0	0	0	0
Left-sided chest pain	0	0	0	0	0	0	0	1	0
Nausea	0	0	0	0	0	0	0	0	2
Pain in extremity, right arm	0	0	0	0	0	1	0	0	0
Skin eruption, neck and trunk	0	0	0	0	1	0	0	0	0
Sweating	0	0	0	0	0	0	0	0	1
Vessel puncture site erythema, right	0	0	0	0	0	0	2	0	0
Total for each dose group n (N)	1 (1)	2 (2)	1 (1)	1 (1)	1 (1)	1 (1)	2 (2)	1 (1)	3 (6)

N = number of subjects; N = number of events; IV = intravenous.

drug, 1 AE occurred in 1 (16.67%) subject in the placebo group. For PO administration, no AEs were reported. The most frequent AEs in the study were infusion site–related AEs, and they increased in frequency with increasing dose, especially between the doses of 800 and 1200 mg. Infusion site–related AEs comprised paraesthesia in 3 subjects (1 subject in the 400-mg IV group and 2 subjects in the 1200-mg IV group), pain in 2 subjects (1 subject in the 800-mg 60-min IV group and 1 subject in the 1200-mg IV group), and phlebitis in 1 subject (200-mg IV group), which the investigator classified as (considered) unrelated to the study drug. Pains and phlebitis of these AEs were reported as the VIP score 1. AEs not related to the infusion site included nausea in 2 subjects (1200-mg IV group), vessel puncture site erythema in 2 subjects (800-mg/30-min IV group), and acne (200-mg IV group), forearm bruise (placebo), skin eruption (800-mg/60-min IV group), left-sided chest pain (800-mg/30-min IV group), and sweating (1200-mg IV group) in 1 subject each.

The severity of AEs was mild in all groups excluding the 1200-mg group, in which 2 participants discontinued drug administration prematurely due to moderate nausea. All subjects recovered without treatment during the observation period except 2 subjects. Although the AEs were not completely resolved by the end of the study, follow-up for the subjects was not required after the last visit because the events were not clinically significant. Eight of the AEs were considered doubtful to be related to the study drug. Of these, 1 AE was considered possibly drug related (infusion site paraesthesia), and 7 were considered probably drug related (2, 2, 1, 1, and 1 case of nausea, infusion site paraesthesia, infusion site pain, pain in the extremities, and sweating, respectively). Apparent differences were not observed regarding the numbers of AEs among the treatment groups ($P = 0.4142$), whereas the frequency of adverse drug reactions (ADRs) significantly differed among the treatment groups ($P = 0.01161$). However, excluding the 1200-mg dose, the ADR count was not significantly different according to the treatment group. No clinically meaningful changes in vital signs, ECG findings, laboratory test results, or physical examination findings were observed.

PHARMACOKINETIC VARIABLES

Single Ascending Dose Study

The mean plasma concentrations of LCB01-0371 after a single IV infusion are shown in Figure 2; the plasma pharmacokinetic parameters are presented in Table II. The median T_{max} of LCB01-0371 after the IV infusion was primarily associated with the length of infusion, ranging from 0.75 to 1.00 h for the 60-min infusion groups and 0.51–0.52 h for the 30-min infusion groups. The mean $t_{1/2}$ ranged from 1.48 to 1.68 h for all IV doses. $V_{d,ss}$ ranged from 57.74 to 76.72 L and was dose independent. The CL ranged from 33.17 to 43.31 L/h and was generally dose independent.

Although the dose proportionalities of AUC_{0-last} and $AUC_{0-\infty}$ were evaluated for all IV dosing groups, a dose proportionality assessment of C_{max} was performed only for the 60-min infusion groups because the 30-min groups did not have sufficient data for a separate analysis. Dose proportionality was evaluated for C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ using a power model (ln [concentration] = $\beta 0 + \beta 1 \times$ ln [dose]). The point estimation and 90% CIs were estimated and presented for the slope ($\beta 1$) of the model (Figure 3). When evaluated using the power model, the estimated slope parameters of C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ were 1.02 (90% CI, 0.89–1.16), 1.05 (90% CI, 0.92–1.17), and 1.04 (90% CI, 0.92–1.67), respectively. Hence, LCB01-0371 after a single IV dose exhibited pharmacokinetic properties that were linearly related to the dose over the tested dose range. In addition, when the infusion time was reduced from 60 to 30 min at the same dose (ie, 800 mg), the mean C_{max} was increased 1.37-fold and the median T_{max} was decreased ~2-fold compared with the values for the 60-min infusion time, whereas the mean AUC_{0-last}, $AUC_{0-\infty}$, CL, $V_{d,ss}$, and $t_{1/2}$ were largely unchanged. AUC_{0-last} and $AUC_{0-\infty}$ were reduced by 0.9-fold, CL and $V_{d,ss}$ were increased by 1.08- and 1.03-fold, and $t_{1/2}$ was decreased by 0.98-fold.

After a single IV infusion, f_e in urine ranged from 7% to 10% of the administered dose (200–1200 mg), and CL_R ranged from 2.50 to 3.49 L/h across groups and exhibited dose independence (Table II). When the infusion time was reduced from 60 to 30 min for the dose of 800 mg, f_e and CL_R were clearly decreased because A_e was

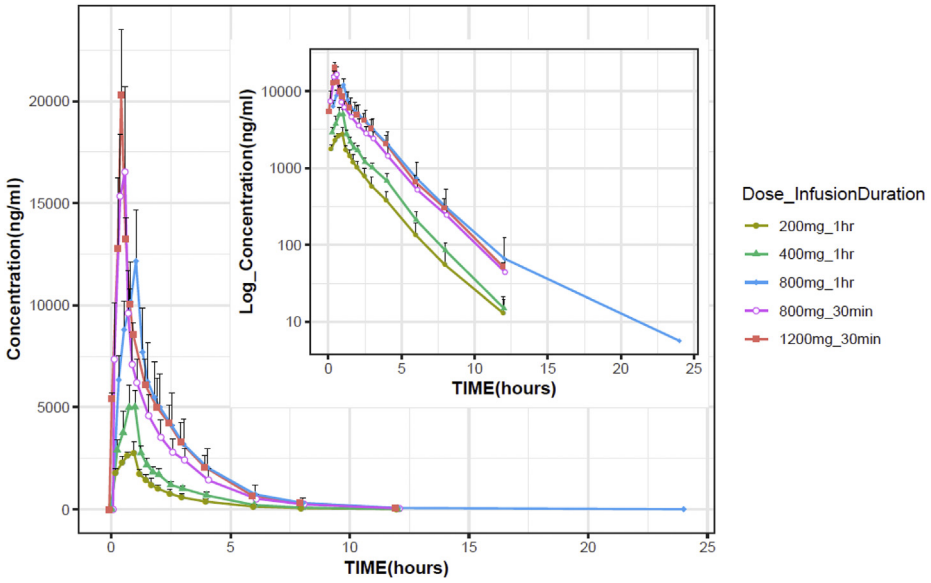

Figure 2. Mean plasma concentration profile after a single intravenous infusion of 200, 400, 800, or 1200 mg of LCB01-0371 using 2 different infusion regimens presented as a linear or log scale that is inserted into the linear scale plot. Error bars denote SDs (n = 6 for 200, 400, and 800 mg; n = 2 for 1200 mg).

markedly diminished, whereas the plasma exposure (AUC_{0-last}) was unchanged.

Absolute Bioavailability Study

The mean plasma concentration–time profiles of LCB01-0371 after an IV infusion of 400 mg or a PO dose of 800 mg are shown in Figure 4, and the pharmacokinetic parameters of LCB01-0371 are presented in Table III. The plasma concentration of LCB01-0371 declined in a relatively similar manner between IV and PO doses, with $t_{1/2}$ values of 1.48 and 1.61 h, respectively. The statistical summary regarding the pharmacologic equivalence between the 2 formulations is presented in Table IV. Equivalence of the dose-normalized total exposure (AUC_{0-last}/dose and $AUC_{0-\infty}$/dose) after IV (reference) or PO (test) administration of LCB01-0371 was determined because the 90% CI of geometric least squares mean ratios fell within the conventional bioequivalence range of 80%–125% (86.6%–110% for AUC_{0-last} and 86.6%–111% for $AUC_{0-\infty}$). The mean absolute bioavailability of LCB01-0371 calculated by using $AUC_{0-\infty}$ was 99.75% after oral administration, indicating similar exposure between IV and PO administration. Sequence and study period effects were not statistically significant. The dose-normalized C_{max} was not bioequivalent between IV and PO administration because the geometric mean ratios between the test and reference formulations were outside the 80%–125% interval (50.0%–105%).

DISCUSSION

The present study examined the safety, tolerability, and pharmacokinetic properties of LCB01-0317 after a single IV administration and investigated the absolute oral bioavailability of the drug after a single IV or PO administration. LCB01-0371 generally exhibited a good safe and tolerability profile after IV dosing at doses of 800 mg using 2 different infusion regimens. However, in the 1200-mg group, 2 subjects receiving the active drug prematurely discontinued treatment due to moderate nausea, and additional treatment or dose escalation was stopped. Thus, the maximum tolerated dose (MTD) could be considered 800 with a 30-min IV infusion of LCB01-0371 in humans.

The AEs in the present study were generally mild, excluding 2 cases of nausea in subjects in the 1200-

Table II. Plasma and urine pharmacokinetic variables after a single intravenous infusion of LCB01-0371. All parameters are expressed as the mean (SD) excluding T_{max}, which is presented as the median (range).

Parameter	Dose/Infusion Duration				
	200 mg/60 min	400 mg/60 min	800 mg/60 min	800 mg/30 min	1200 mg/30 min
	(n = 6)	(n = 6)	(n = 6)	(n = 6)	(n = 2)
C_{max}, ng/mL	2923.05 (456.73)	5247.97 (957.78)	12,161.26 (2486.04)	16,691.12 (4052.69)	20,310.18 (3217.71)
T_{max}, h	0.75 (0.75–1.02)	0.75 (0.75–1.03)	1.00 (0.75–1.02)	0.51 (0.33–0.52)	0.52 (0.52–0.52)
AUC_{0-last}, ng · h/mL	5598.48 (980.45)	9392.11 (1454.92)	25,716.27 (8113.56)	3049.42 (5157.55)	28,604.2 (2672.15)
$AUC_{0-\infty}$, ng · h/mL	5631.09 (1001.53)	9424.3 (1459.21)	25,807.57 (8117.29)	23,155.09 (5210.41)	28,723.73 (2673)
$t_{1/2}$, h	1.68 (0.17)	1.48 (0.06)	1.66 (0.35)	1.62 (0.14)	1.59 (0.15)
$V_{d,ss}$, L	57.74 (3.46)	67.54 (13.05)	58.07 (8.39)	59.74 (10.09)	76.72 (2.51)
$V_{d,z}$, L	87.48 (11.89)	92.48 (13.57)	76.39 (9.93)	83.1 (13.67)	96.5 (18.06)
CL, L/h	36.43 (6.23)	43.31 (6.5)	33.17 (8.47)	35.84 (7.03)	41.96 (3.9)
A_e, mg	19.09 (7.42)	30.46 (5.4)	80.27 (25.47)	56.58 (16.58)	98.85 (5.59)
CL_R, L/h	3.49 (1.37)	3.29 (0.62)	3.23 (1.01)	2.5 (0.72)	3.46 (0.13)
f_e	0.09 (0.04)	0.08 (0.01)	0.1 (0.03)	0.07 (0.02)	0.09 (0.01)

A_e = amount of unchanged drug in urine from the time of dosing to the last measurable concentration; CL = clearance; CL_R = renal clearance; f_e = fraction of dose recovery unchanged in urine; $V_{d,ss}$ = volume of distribution at steady state; $V_{d,z}$ = volume of distribution during terminal phase.

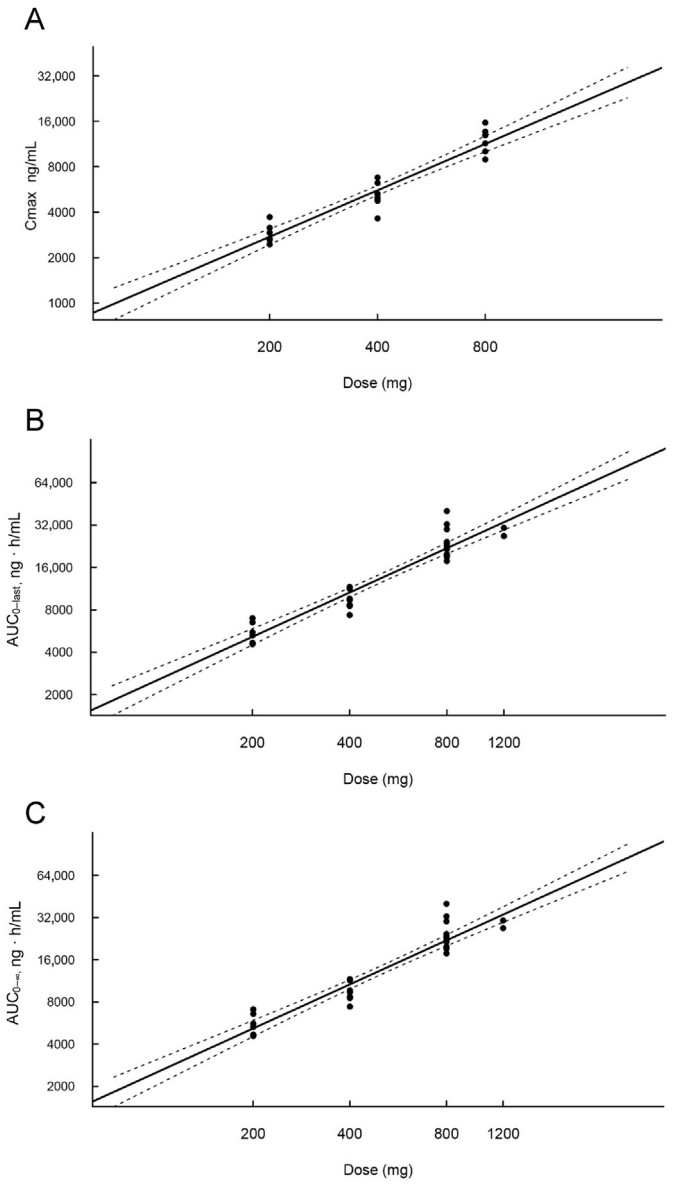

Figure 3. Individual values for ln (C_{max}), ln (AUC_{0-last}) and ln (AUC_{0UC}) versus ln (dose) after a single intravenous infusion (A, B, and C) of LCB01-0371. The solid lines represent the least squares regression line, and the dashed lines represent the 90% CI of the linear regression.

mg group. Gastrointestinal AEs such as nausea were commonly observed at doses exceeding the MTD in previous Phase I studies of single or multiple oral dosing of LCB01-0371.[22] No treatment- or dose-related increase in the frequency of reported AEs or ADRs was observed at doses less than the MTD. The most common drug-related AEs were infusion site–related AEs such as infusion site paraesthesia and pain. There were no clinically relevant abnormalities in terms of vital signs, physical examination, ECG findings, or laboratory tests. The safety and tolerability profiles were similar to those in a single-dose IV infusion study of the currently marketed oxazolidinones linezolid and tedizolid.[23,24]

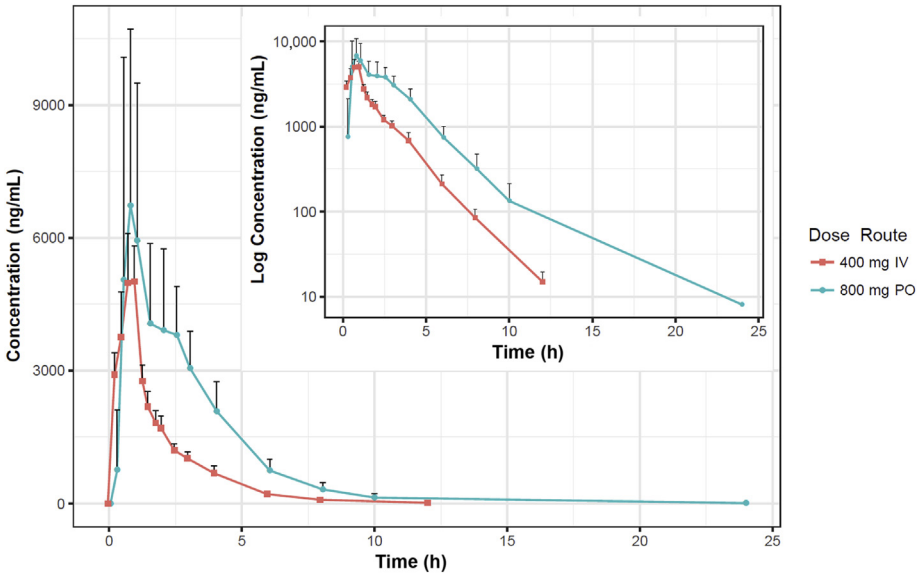

Figure 4. Mean plasma concentration profile after a single intravenous (IV) infusion (400 mg) or single oral (PO) administration (800 mg) of LCB01-0371 presented as a linear or log scale that is inserted into the linear scale plot. Error bars denote SDs (n = 8 for each administration group).

Moreover, no abnormal hematologic changes potentially caused by reversible myelosuppression, a primary safety concern for the oxazolidinone class, were observed for any tested dose. These results are consistent with the tolerability findings from a recently published Phase I study in which the mean relative changes from baseline of all hematologic values after 21 days of oral LCB01-0371 administration at doses ranging from 800 mg once daily to 1200 mg BID were not significantly different among the doses, including placebo.[20]

After a single IV administration, LCB01-0371 exhibited linear pharmacokinetic properties for the range of 200−800 mg regardless of the infusion regimen; $t_{1/2}$, V_d, and CL were unchanged over the corresponding dose range, and C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ increased proportionally with increasing IV doses. Similar to these findings, LCB01-0371 after a single PO administration exhibited linear pharmacokinetic properties and dose-proportional systemic exposure over the range of 50−800 mg.[22] However, after a single PO administration of doses >800 mg, a lack of dose proportionality was noted, and CL/F, V_d/F, and $t_{1/2}$ tended to decrease or increase with increasing doses, suggesting nonlinear pharmacokinetic properties via a saturable absorption or elimination mechanism.

With respect to the different infusion regimens, shortening the infusion time from 60 to 30 min increased C_{max} by 1.37-fold and decreased T_{max} by ~2-fold, whereas AUC_{0-last}, $AUC_{0-\infty}$, CL, $V_{d,ss}$, and $t_{1/2}$ were unchanged. A higher C_{max} with a shorter IV infusion length may be disadvantageous because the occurrence of more AEs and the risk for infusion site−related complications have been generally implicated with higher peak exposures and enhanced infusion rate. In addition, shortened infusion times should not be correlated with clinical efficacy because the activity of LCB01-0371 was not time dependent according to a thigh infection mouse model (data not shown). Nonetheless, shortening the dosing time will lead to higher peak concentrations, without loading unnecessary volume. In the same situation, A_e was markedly diminished from ~80 to 56, likely because of the large interindividual variability of renal excretion in the 800-mg/60-min IV group in which 2 subjects had ~2-fold higher values (~120 mg) than the other subjects (~60 mg).

Table III. Pharmacokinetic parameters of LCB01-0371 after a single intravenous (IV) infusion or a single oral (PO) administration. All parameters are expressed as the mean (SD) excluding T_{max}, which is presented as the median (range).

Parameter	Dose/Infusion Duration	
	LCB01-0371 IV 400 mg/1 h	LCB01-0371 PO 800 mg
	(n = 8)	(n = 8)
$AUC_{0-\infty}$, ng · h/mL	9424.3 (1459.21)	18,846.5 (4980.67)
AUC_{0-last}, ng · h/mL	9392.11 (1454.92)	18,636.27 (4877.66)
C_{max}, ng/mL	5247.97 (957.78)	8197.48 (3469.27)
T_{max}, h	0.75 (0.75–1.03)	0.88 (0.5–3.0)
F_I, %	–	99.75 (20.59)
F_L, %	–	98.99 (20.19)

F_I = bioavailability calculated for each subject as ($AUC_{0-\infty}$ after PO) × (IV dose) × 100/($AUC_{0-\infty}$ after IV) × (PO dose); F_L = bioavailability calculated for each subject as (AUC_{0-last} after PO) × (IV dose) × 100/(AUC_{0-last} after IV) × (PO dose).

Table IV. Statistical analysis of bioequivalence after a single intravenous (IV) infusion or a single oral (PO) administration of LCB01-0371.

Parameter	No. of Subjects	Geometric Least Squares Mean (90% CI)	Ratio Geometric Least Squares Mean, PO/IV, (90% CI)
Dose-normalized AUC_{0-last}, ng · h/mL			
PO	8	22.59 (20.66–24.70)	0.97 (0.86–1.10)
IV (60-min infusion)	8	23.24 (21.26–25.41)	
Dose-normalized $AUC_{0-\infty}$, ng · h/mL			
PO	8	22.83 (20.88–24.97)	0.98 (0.86–1.11)
IV (60-min infusion)	8	23.32 (21.32–25.51)	
Dose-normalized C_{max}, ng/mL			
PO	8	9.36 (7.22–12.14)	0.72 (0.50–1.05)
IV (60-min infusion)	8	12.92 (9.96–16.76)	

For oxazolidinone antibiotics, the AUC/MIC ratio has been correlated with bacteriostatic activity.[25–28] LCB01-0371 activity was also most reliably associated with the AUC/MIC ratio in a thigh infection mouse model against methicillin-susceptible *S aureus* (MSSA) (data not shown). Compared with linezolid, LCB01-0371 has exhibited similar or lower MICs for gram-positive pathogens, including MSSA, in in vitro and in vivo studies.[16] In the previous clinical trial, the AUC for linezolid was six or higher than that of LCB01-0371 when they are orally administered at the similar dose.[22] Therefore, higher exposures of LCB01-0371 are required to achieve similar AUC/MIC ratios to linezolid although reference criteria for AUC/MIC ratios to assess bacteriostatic activity of LCB01-0371 have not been reported.

LCB01-371 exhibited high absolute bioavailability of 99.75% in subjects who received a dose of 800 mg, which is the dose currently used in Phase II studies. The total exposures (AUC_{0-last} and $AUC_{0-\infty}$) of LCB01-0371 were bioequivalent after IV and PO dosing. However, the C_{max} of the PO formulation was lower than that of IV formulation, and the peak

exposure was not bioequivalent. A lack of equivalence for peak exposure is not considered clinically important because the efficacy of LCB01-0371 is best correlated with the AUC/MIC ratio. LCB01-0371 has potent activity against gram-positive pathogens, including MSSA and MRSA.[16] The MIC_{90} of both the MSSA and MRSA isolates by LCB01-0371 was 2 μg/mL, and the human plasma protein binding of LCB01-0371 is ~37%. On the basis of this information, Table V summarizes the statistics regarding the pharmacologic equivalence of $fAUC_{0-last}$ (area under the unbound plasma concentration versus time curve from the time of dosing to the last measurable concentration)/MIC or $fAUC_{0-\infty}$ (area under the unbound plasma concentration versus time curve from the time of dosing to infinity)/MIC between IV and PO, indicating that $fAUC_{0-last}$/MIC and $fAUC_{0-\infty}$/MIC are bioequivalent between 2 formulations. This high oral bioavailability provides support for the ability to switch between IV and PO formulations without dose adjustment or a loading dose. The ability to switch between formulations may reduce the duration of hospitalization and the treatment cost for some patients.

Despite the high bioavailability of LCB01-0371, the MTD after a single IV administration (800 mg) was much lower than that after a single PO administration (2400 mg).[22] This finding is likely because the normalized C_{max} after IV dosing was much higher than that after PO dosing, whereas normalized AUC_{0-last} and $AUC_{0-\infty}$ were almost identical between the 2 formulations. A higher C_{max} was closely associated with AEs, especially gastrointestinal AEs such as nausea, in the present study as well as in previous research. In addition, the nonlinear pharmacokinetic properties of LCB01-0371 after a single PO administration at doses >800 mg are also likely to contribute to the difference in the MTD between the 2 formulations.

One limitation of the present study was the relatively short follow-up period (7–9 days) and the limited number of enrolled subjects, which may have excluded the reporting of certain AEs. Further evaluation in larger populations will provide a more exact safety profile of IV LCB01-0371. Another limitation of the study was the study design restricted to investigating the safety margin after IV administration of LCB01-0371. After investigating 800 mg over a 30-min or 60 min IV infusion, we did not try 1200 mg over 60 min, 1000 mg over 30 min, or 1000 mg over 60 min, and so forth (which may expand the safety margin and provide further information for LCB01-0371) but performed an infusion of 1200 mg over 30 min. Eventually, the MTD of IV LCB01-0371 was determined as 800 mg over 30 min.

CONCLUSIONS

A single IV infusion of LCB01-0371 was generally safe and well tolerated up to a dose of 800 mg over a 30-min infusion. The systemic exposures of LCB01-0371 were dose proportional, and the pharmacokinetic parameters remained unchanged regardless of the dose for IV administration, indicating linear pharmacokinetic properties over the tested dose range. The total

Table V. Statistical analysis of bioequivalence of $fAUC$/MIC after a single intravenous (IV) infusion or a single oral (PO) administration of LCB01-0371.

Parameter	No. of Subjects	Geometric Least Squares Mean (90% CI)	Ratio of Geometric Least Squares Mean, PO/IV (90% CI)
Dose-normalized $fAUC_{0-last}$/MIC			
PO	8	0.00732 (0.00670–0.00800)	0.97 (0.86–1.10)
IV (60-min infusion)	8	0.00712 (0.00651–0.00778)	
Dose-normalized $fAUC_{0-\infty}$/MIC			
PO	8	0.00735 (0.00672–0.00803)	0.98 (0.86–1.11)
IV (60-min infusion)	8	0.00719 (0.00658–0.00787)	

$fAUC_{0-last}$ = area under the unbound plasma concentration versus time curve from the time of dosing to the last measurable concentration; $fAUC_{0-\infty}$ = area under the unbound plasma concentration versus time curve from the time of dosing to infinity.

exposures of LCB01-0371 were equivalent between IV and PO administration, and their parameters were comparable, suggesting that the route of administration can be switched without dose adjustment.

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CONFLICTS OF INTEREST

This study was funded by LegoChem Biosciences, Inc. Dr. Y.L. Cho and Dr. Nam are employees of LegoChem Biosciences, Inc. They contributed to the study design or revision of the manuscript. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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