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# Safety, tolerability and pharmacokinetics of 21 day multiple oral administration of a new oxazolidinone antibiotic, LCB01-0371, in healthy male subjects

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**Background:** LCB01-0371 is a new oxazolidinone antibiotic, which targets most Gram-positive organisms. High rates of adverse reactions including myelosuppression have been reported for existing oxazolidinones, limiting their long-term use.

**Objectives:** The safety, tolerability and pharmacokinetics (PK) of 21 day multiple oral administrations of LCB01-0371 in healthy male subjects (clinicaltrials.gov: NCT02540460) were investigated.

**Methods:** In this randomized, double-blind, placebo-controlled study, subjects received 800 mg of LCB01-0371 once or twice daily or 1200 mg of LCB01-0371 twice-daily for 21 days in a fasting state. Safety and tolerability profiles including laboratory tests were evaluated during the study and on a post-study visit and the results were analysed using repeated-measures analysis of variance (RM-ANOVA). Serial blood samples for PK analysis were collected up to 12 h after dosing on day 21.

**Results:** A total of 40 subjects were enrolled and 34 subjects completed the study. Two subjects dropped out according to stopping rules. In the 1200 mg twice-daily dose group, the absolute value of red blood cell count, haematocrit and haemoglobin decreased by $500\times10^6$/L (6.5%), 4.5% (6.8%) and 1.6 g/dL (6.9%), respectively, after 21 day administrations of LCB01-0371. However, mean relative changes from baseline of all haematology values were not significantly different among doses, including placebo (all, $P < 0.05$). PK profiles of LCB01-0371 in the dose range of 800 mg once daily to 1200 mg twice daily were consistent with previous studies.

**Conclusions:** LCB01-0371 is well tolerated in healthy male subjects with comparable haematology profiles to placebo, after multiple doses of up to 1200 mg twice daily for 21 days.

## Introduction

Oxazolidinones are a class of antibiotics containing a five-member heterocyclic ring in their structure. They exert bacteriostatic microbial activity by inhibiting protein synthesis via direct binding to the bacterial ribosomal subunit.[1] Oxazolidinones are known to have strong activity against nearly all Gram-positive organisms, including those with resistance to other antibiotics.[2,3] In 2000, linezolid (Zyvox) became the first FDA-approved drug in the class and it is used as the current treatment option against Gram-positive bacteria, including staphylococci (e.g. MRSA), streptococci and enterococci (e.g. VRE).[4–6] Following this, tedizolid was approved by the FDA in 2014 and several more oxazolidinones have been subsequently discovered.[5]

Although they are generally safe when used in the recommended dosage regimen, earlier oxazolidinone agents were reported to affect the haematopoietic system in some cases, especially in patients who were administered the drug for 14 days or more.[6–8] Linezolid may cause reversible myelosuppression, such as thrombocytopenia, anaemia or leukopenia, with prolonged (>14 days) drug exposure and dosing, especially in patients with pre-existing myelosuppression.[6,9] Oxazolidinones are used to treat serious infections and patients administered the drug are often susceptible to its myelosuppressive side effects. Therefore, safety and tolerability are critical issues to consider when prescribing these antibiotics.

Previously, several studied have reported the relationship between oxazolidinone and haematological toxicity. Lin *et al.*[10]

reported that severe linezolid-induced thrombocytopenia was relatively common in patients with renal insufficiency and Sasaki *et al.*[11] developed a population pharmacokinetic (PK)–toxicodynamic model of linezolid and thrombocytopenia. Boak *et al.*[12] also reported that linezolid therapy for a long duration (>10 days) was the most important predictor of linezolid toxicity, using a population PK–toxicodynamic model. For tedizolid, Lodise *et al.*[13] conducted a 21 day multiple dose study in healthy volunteers and showed that higher tedizolid doses may adversely impact haematological parameters.

LCB01-0371 is a new oxazolidinone, which has shown high solubility and good absorption, distribution, metabolism, excretion, toxicity and PK profiles in animal studies.[3] Its enhanced potency compared with that of linezolid has been demonstrated in both Gram-positive and -negative bacteria including MSSA and MRSA strains, *in vitro* and in animal studies.[3] The aim of this study was to assess its safety and tolerability with a focus on haematological changes and to investigate the PK following a 21 day multiple oral administration of LCB01-0371 in healthy male subjects.

## Patients and methods

This study was performed in accordance with the Declaration of Helsinki and Korean Good Clinical Practice. The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB number B-1405/252-003), Seongnam, Korea, and was registered at clinicaltrials.gov (NCT02540460). All subjects provided written informed consent prior to participating in the study.

### Subjects

Healthy male volunteers aged 20–45 years with a BMI of 20.0–27.0 kg/m$^2$ were eligible. The subjects were screened based on medical history, physical examination, 12-lead ECG, vital signs and results of drug abuse and serology tests. Subjects whose liver function test results were 1.5-fold higher than the upper limit of the reference range (1–40 IU/L) or whose white blood cell (WBC; 4.0–10.0×10$^9$/L), red blood cell (RBC; 4.2–6.3×10$^{12}$/L) and platelet (130–400×10$^9$/L) counts or haemoglobin (Hb; 13–17 g/dL) results were below the lower limit of the reference range were excluded. Subjects who had a history of clinically significant cardiovascular, renal, hepatic, pulmonary, gastrointestinal, endocrine, haematological, vascular or collagen disease or who had received an investigational drug within 60 days of the screening date or taken any medication or herbal medication within 14 days of the screening date were also excluded.

### Study drugs

The LCB01-0371 for oral administration (400 mg) and placebo tablets were supplied by LegoChem BioSciences Inc. (Daejeon, Korea). Placebo tablets were identical with LCB01-0371 in size, texture and colour. The manufacturing process was in accordance with good manufacturing process (GMP) standards and the drugs were delivered and stored according to the manufacturer's instructions.

### Study design

This double-blind, placebo-controlled, 21 day multiple-ascending dose study consisted of three LCB01-0371 dosage groups: 800 mg once daily, 800 mg twice daily and 1200 mg twice daily. Twelve subjects were allocated to each dose group (active drug:placebo, 5:1) and each subject was randomized to receive active or placebo drug by an independent panel. The safety and tolerability of the low dosage were confirmed in a safety review meeting prior to progressing to the next dose level.

Subjects in the 800 mg once-daily group received two tablets of LCB01-0371 (400 mg) or placebo from day 1 to day 21 in the morning (21 doses over 21 days) and subjects in the 800 mg twice-daily and 1200 mg twice-daily groups received morning and evening doses of two or three tablets of LCB01-0371 (400 mg) or placebo for 20 days and a morning dose on day 21 (41 doses over 21 days). All doses were administered in a fasted state by the investigators and compliance was 100%.

Serial blood samples for the PK analysis were collected before dosing on days 1, 3, 6, 9, 12, 15, 17, 19 and 20 and at 0 (pre-dosing), 0.5, 1, 2, 4, 8 and 12 h after dosing on day 21. Blood samples (6 mL) were drawn into heparinized tubes. The samples were centrifuged (4 °C, 1800 **g**, 8 min) and three plasma aliquots (0.8 mL) were placed into Eppendorf tubes. The specimens were stored at −70 °C or colder until the analysis.

### Safety assessments

The vital signs, 12-lead ECG, physical examination and recording of adverse events (AEs) were conducted for the safety assessment. The laboratory tests, including haematology, were serially conducted on days 1 (baseline), 3, 6, 9, 12, 15, 17, 19 and 21 prior to drug administration and on a post-study visit. The safety and tolerability profiles were reviewed in all subjects who received LCB01-0371 at least once at each dose level in a safety review meeting prior to progressing to the higher dose level, which was initiated only when the lower doses were found to be safe and well tolerated. The specified trial stopping rules in this study were as follows: WBC count <3.6×10$^9$/L, RBC count <4.2×10$^{12}$/L, absolute neutrophil count (ANC) <1800×10$^6$/L; platelet count <130×10$^9$/L, Hb <13 g/dL, haematocrit (Hct) <39%; prothrombin time [international normalized ratio (INR)] >1.2 and activated partial thromboplastin time >45.0 s.

### PK and statistical analysis

PK analysis was performed for subjects who had full PK data for day 21. The PK parameters of LCB01-0371 were estimated using non-compartmental analysis using Phoenix/WinNonlin (version 6.4, Pharsight Corporation, CA, USA). The $C_{max}$ at steady state ($C_{max,ss}$) and $T_{max}$ at steady state ($T_{max,ss}$) were derived from the observed data. The AUC for the dosing interval at steady state ($AUC_{tau,ss}$) was calculated by using the linear up/log down trapezoidal method. The $t_{1/2}$ and the apparent clearance (CL/F, where F indicates bioavailability) were also calculated.

Safety analysis was performed for subjects who were administered LCB01-0371 at least once. The haematology results were analysed in three ways: (i) haematology values on day 21 in the morning (pre-dose) were converted into relative changes from baseline (day 1) and compared among the dose levels (800 mg once and twice daily, 1200 mg twice daily and the placebo) using the Kruskal–Wallis test; (ii) serial haematology values over 21 days were converted into relative changes from the baseline and repeated-measures analysis of variance (RM-ANOVA) was used to compare the relative changes among the dose levels; and (iii) the AUCs of the time-relative change from baseline of each haematology value were compared among the dose levels. All the statistical analyses of the PK and safety data were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA).

### Determination of plasma concentrations

The plasma LCB01-0371 concentrations were measured in human plasma specimens using a validated LC (Shiseido Nanospace SI-2, Shiseido, Japan) coupled with MS/MS (TSQ Quantum Discovery, Thermo, USA) by BioCore Co., Ltd (Seoul, Korea). Each plasma sample (100 μL) was mixed with 10 μL of internal standard working solution (100 μg/mL) and 1 mL of acetonitrile and vortexed for 2 min. After centrifugation at 13000 rpm for 5 min at 4 °C, supernatant was injected into the LC–MS/MS and separated on a C18 column (3 μm, 2.1×100 mm) with a mobile phase consisting of 1 mM ammonium formate in distilled water/acetonitrile (70/30, v/v) and a flow rate of 0.2 mL/min. The concentrations were quantified by the internal standard

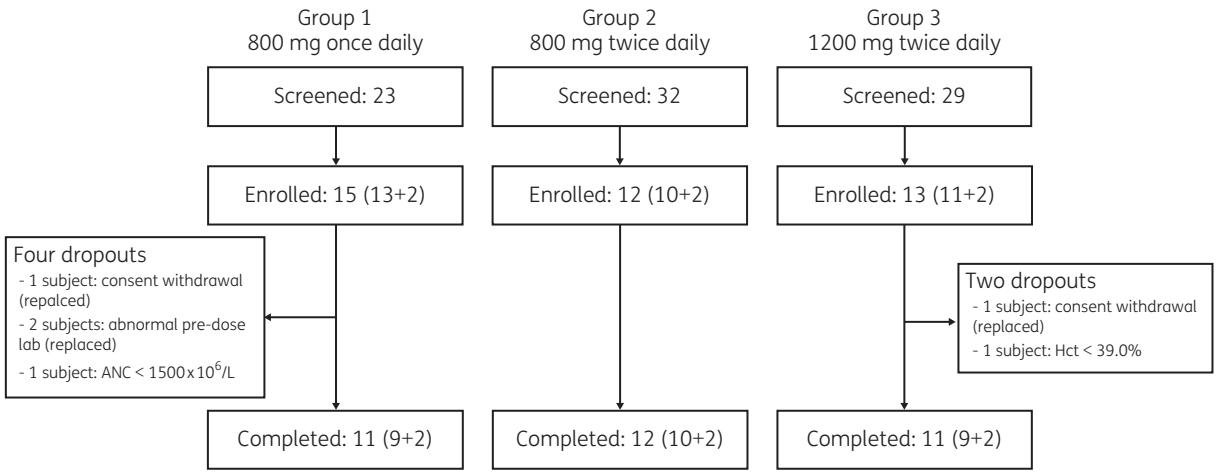


**Figure 1.** Subject disposition. Data are presented as the number of subjects (active drug of LCB01-0371 + placebo).

method and the standard calibration curves were linear over the range of 20–60000 ng/mL ($r^2 > 0.9900$).

## Results

### *Subjects*

Forty healthy male volunteers were enrolled; 13, 10, 11 and 6 subjects were administered 800 mg of LCB01-0371 once daily, 800 mg of LCB01-0371 twice daily, 1200 mg of LCB01-0371 twice daily and placebo (pooled), respectively. Thirty-four subjects (85.0%) completed the study and six subjects stopped early in total. In the 800 mg once-daily group, two subjects dropped out on day 7, after pre-dose laboratory results were recognized as out of the reference range. One subject was replaced after consent withdrawal. Another subject dropped out after ANC of $1200\times10^6$/L was measured and was not replaced. In the 1200 mg twice-daily group, one subject was replaced after consent withdrawal. Another subject was dropped out after Hct of 38.8% was measured and was not replaced. The summary of subject disposition is presented in Figure 1. The mean ± SD age, height and weight were 26.2±3.1 years, 173.8±4.6 cm and 68.5±6.1 kg, respectively. The demographic characteristics were not significantly different over the doses.

### *Haematological and other laboratory tests*

Safety analysis was performed for 13, 10 and 11 subjects in the 800 mg once-daily group, the 800 mg twice-daily group and the 1200 mg twice-daily group, respectively, who were administered active LCB01-0371 drug at least once. Because of the previously known myelosuppressive effects of oxazolidinones, their haematological effects were a particular focus of this study.

The RBC, Hct and Hb values on day 21 were $500\times10^6$/L (6.5%), 4.5% (6.8%) and 1.6 g/dL (6.9%) lower than those on the baseline day in the 1200 mg twice-daily dose group ($P = 0.012$, 0.010 and 0.024, respectively). The other parameters showed no significant difference among the dose levels. The key haematology values at baseline and day 21 are presented in Table 1.

For serial analysis, relative changes from the baseline of haematology values across time were evaluated using RM-ANOVA. Most of the key haematology values decreased, with minimal changes over the 21 days (Figure 2). When serial relative changes from baseline were compared using RM-ANOVA, differences in relative changes were not significant among the dose levels over time. Mean serial relative changes in the platelet count and ANC from the baseline throughout the study period (21 days) ranged from 0.85 to 1.06 and from 0.72 to 1.13, respectively, and the difference in relative change from the baseline at each dose was not statistically significant ($P = 0.441$ and 0.366, respectively) among doses. For WBC, RBC, Hb and Hct, the ranges of relative changes were 0.73–1.03, 0.85–1.06, 0.84–1.09 and 0.83–1.08, respectively, and the changes from baseline were similar among the dose levels throughout the study ($P = 0.286$, 0.599, 0.368 and 0.083, respectively). Additionally, the AUCs of the relative changes from baseline of haematology values were not significant over dose levels (Figure 2).

Application of the stopping rules led to two subjects withdrawing from the study. One subject received 800 mg of LCB01-0371 once daily for 5 days and dropped out of the study after a decreased ANC level ($1200\times10^6$/L) was identified on day 6, which was lower than the margin of the stopping rule ($1800\times10^6$/L). No other significant finding was reported and the ANC recovered to the reference range on day 22. The other subject received 1200 mg of LCB01-0371 twice daily for 16 days and a decreased Hct (38.8%), which was lower than the margin of the stopping rule (39%), and marginally decreased platelet count ($153\times10^9$/L) were observed on day 17. This subject also had increased AST and ALT >1.5 times the upper limit of the reference range at the same time (up to 107 and 239 IU/L, respectively) and dropped out on day 17. Hct decreased to 35.5% on day 19. The haematology results recovered to the reference range in the follow-up test after day 30.

Another subject who completed the 800 mg twice daily dosing schedule showed decreased ANC ($1060\times10^6$/L) on day 21 after the final dose, which recovered ($2968\times10^6$/L) the next day. The decreased neutrophil count was reported as either moderate or severe adverse drug reactions (ADRs) and all values recovered

**Table 1.** Key haematology values at baseline and day 21 after multiple administrations of LCB01-0371 for 21 days

| | 800 mg once daily ($n = 13$) | | 800 mg twice daily ($n = 10$) | | 1200 mg twice daily ($n = 11$) | | Placebo ($n = 6$) | |
|---|---|---|---|---|---|---|---|---|
| Parameter[a] | baseline | day 21 | baseline | day 21 | baseline | day 21 | baseline | day 21 |
| WBC count ($\times 10^9$/L) | 5.96±1.28 | 5.05±1.39 | 6.88±0.61 | 5.06±1.24 | 6.85±1.32 | 5.63±1.02 | 6.16±0.47 | 4.91±1.09 |
| ANC ($\times 10^6$/L) | 3097±1047 | 2404±974 | 3654±825 | 2607±1018 | 3699±832 | 3037±634 | 3152±566 | 2616±1051 |
| Platelet count ($\times 10^9$/L) | 245±33 | 242±56 | 259±49 | 218±33 | 239±45 | 220±40 | 217±28 | 210±15 |
| RBC count ($\times 10^{12}$/L) | 4.99±0.24 | 4.68±0.13 | 4.96±0.27 | 4.74±0.24 | 5.19±0.4 | 4.7±0.32 | 5.1±0.32 | 4.94±0.32 |
| Hct (%) | 43.4±1.7 | 41.2±1.3 | 44±2.4 | 41.3±2.5 | 46.7±2.4 | 42.2±2.6 | 45.6±2.2 | 43.8±3 |
| Hb (g/dL) | 15.5±0.8 | 14.7±0.5 | 15.1±1.1 | 14.3±1.2 | 16.2±1.1 | 14.6±1.1 | 15.7±0.9 | 15.2±1.2 |

Data are presented as mean ± SD.
[a]PK analysis was conducted in subjects who completed PK samplings.

by the end of the study. Other haematology values were within normal range.

There were no clinically important changes from the baseline in other laboratory test items or vital signs, ECG and physical examinations.

### *AEs*

Fifty-two AEs were observed in 24 subjects and 45 events occurred in 19 subjects who received the active drug (Table 2). The majority (>90%) of ADRs were considered mild in intensity and patients recovered with no intervention and severe AE was not reported. Diarrhoea, dyspepsia, headache and nausea were commonly reported ADRs and the frequencies of ADRs tended to increase as the LCB01-0371 dose increased (30.8%, 40.0% and 63.6% of subjects administered 800 mg once daily, 800 mg twice daily and 1200 mg twice daily, respectively).

### *PK*

PK analysis was performed for 9, 10 and 9 subjects in the 800 mg once-daily group, the 800 mg twice-daily group and the 1200 mg twice-daily group, respectively, who completed PK samplings and had valid plasma concentrations. LCB01-0371 was rapidly absorbed and reached the $C_{max,ss}$ at 0.5–1 h on average. The elimination was monophasic, with $t_{1/2}$ values of 1.3–2.1 h, and the differences in the $t_{1/2}$ values among the groups were not statistically significant ($P = 0.089$). The $AUC_{tau,ss}$ and $C_{max,ss}$ of each dose group are presented in Table 3 and Figure 3. The $C_{min}$ at steady state ($C_{min,ss}$) was <1% of the $C_{max,ss}$ and accumulations were minimal following the 21 day multiple administrations.

## Discussion

This study mainly focused on long-term safety of LCB01-0371. Thus, the haematology tests were serially performed and analysed every 2 or 3 days from baseline to day 21. The analyses, including RM-ANOVA and comparison of AUCs of the relative changes that reflect serial changes, provided a better understanding of the course of changes than simple comparison of baseline and day 21 values.

The haematological effects of prolonged oxazolidinone therapy are associated with their mechanism of action. In bacterial cells, these drugs exert their effect by binding to the 50S subunit of the bacterial ribosome and inhibiting protein synthesis.[14,15] Similarly, in human cells, oxazolidinones inhibit mitochondrial protein synthesis, probably by directly binding to the large subunit of the mitochondrial ribosome.[16–18] This toxic mechanism is known to be duration-dependent, especially in 10 day regimens. It is clinically significant because the majority of patients receive linezolid every 8 or 12 h for 10–14 days according to drug labels.[19,20] As the current study only included a negative control (placebo) group and lacked a positive control group, the result was compared with another study with similar 21 day multiple doses of linezolid, tedizolid or placebo. The decline in haematology values for the LCB01-0371 800 mg twice-daily dose, which is the expected standard therapeutic dose level, was similar to those for standard doses of tedizolid and linezolid. An average of 6% decrement and a maximum of 15% decrement in haematology values, including platelet count, were observed after 21 day multiple administrations of LCB01-0371, whereas average decrements of 22% and 23% were observed for linezolid 600 mg twice daily and tedizolid 300 mg once daily, respectively.[13] However, comparisons with other oxazolidinones from the literature must be made with caution because study designs, conditions and statistical analytical methods may be different.

Also, the serial haematological analysis indicated that the overall trend and range of change of the haematology values were generally similar among the dose levels. Results from RM-ANOVA of serial haematology values and comparison of AUCs of the relative changes (Figure 2) suggest that significances of the group differences in haematological effects were rather low in healthy subjects. In these results, decreases in haematology values were only slightly related to the dose of LCB01-0371. Exploration of the dose–toxicity relationship using modelling is warranted in further studies for prediction of toxicity.

Our results suggest that oral doses of LCB01-0371 administered for 21 days were well tolerated in healthy subjects at doses of up to 1200 mg twice daily. Diarrhoea, dyspepsia, headache and nausea were the most common ADRs and were mild in intensity. These symptoms are frequent and non-specific after oral doses of numerous antibiotics and are generally terminated when the antibiotic is discontinued.[10] In addition, the frequency of the ADRs at the 800 mg twice-daily dose was less than half of that at the 1200 mg twice-daily dose, which is expected to be a

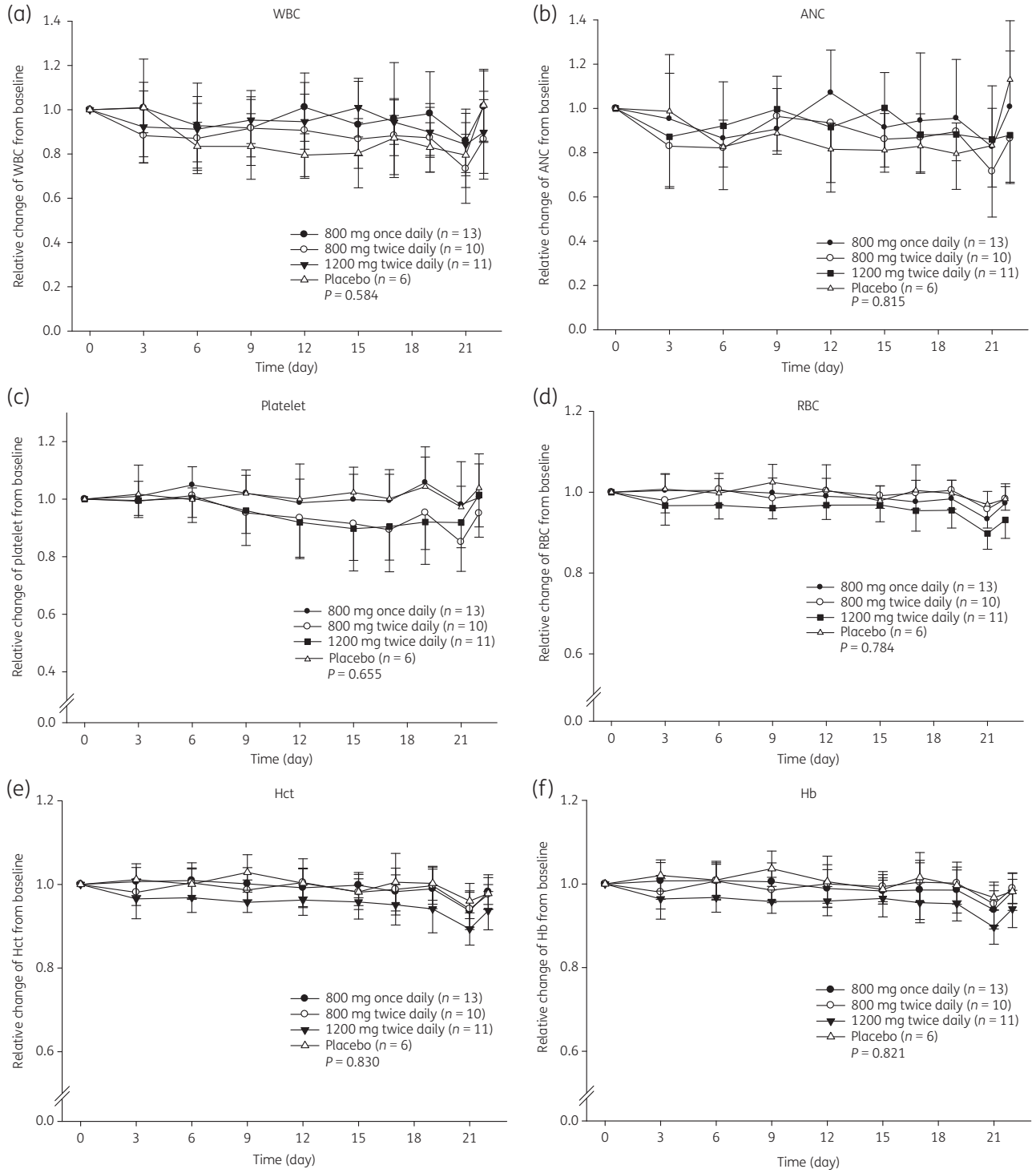


**Figure 2.** Relative change from baseline in (a) WBC count, (b) ANC, (c) platelet count, (d) RBC count, (e) Hct and (f) Hb from baseline (pre-dose) during 21 day multiple administrations of LCB01-0371. Safety analysis was conducted in subjects who were administered LCB01-0371 at least once. *P* values for ANOVA in AUCs of the baseline-normalized haematology values versus time among doses are also presented.

supratherapeutic dose. An ADR with moderate intensity at the 1200 mg twice-daily LCB01-0371 dose was experienced by a subject who dropped out after exhibiting elevated liver enzymes and a decreased Hct. The $C_{min}$ range on days 3–17 was 1157.0–3044.5 ng/mL, which was at least 10-fold higher than that of other subjects given the same dose. As in the cases of linezolid and tedizolid,[8,21] the high drug concentration and high exposure to the drug may have been responsible for the ADR in this subject.

**Table 2.** AEs after multiple administrations of LCB01-0371 for 21 days

| AE | 800 mg once daily ($n = 13$) | 800 mg twice daily ($n = 10$) | 1200 mg twice daily ($n = 11$) | Total ($n = 34$) |
|---|---|---|---|---|
| Any TEAE | 7 [5] (38.5) | 5 [5] (50.0) | 33 [9] (81.8) | 45 [19] (55.9) |
| Any ADR | 6 [4] (30.8) | 4 [4] (40.0) | 22 [7] (63.6) | 32 [15] (44.1) |
| abdominal discomfort | | | 2 [2] (18.2) | 2 [2] (5.9) |
| asthenia | | | 2 [2] (18.2) | 2 [2] (5.9) |
| diarrhoea | 1 [1] (7.7) | | 6 [5] (45.5) | 7 [6] (17.6) |
| dizziness | 1 [1] (7.7) | 1 [1] (10.0) | | 2 [2] (5.9) |
| dyspepsia | | 2 [2] (20.0) | 1 [1] (9.1) | 3 [3] (8.8) |
| ear swelling | 1 [1] (7.7) | | | 1 [1] (2.9) |
| feeling cold | 1 [1] (7.7) | | | 1 [1] (2.9) |
| haematological test abnormal | | | 1 [1] (9.1) | 1 [1] (2.9) |
| headache | 1 [1] (7.7) | | 2 [2] (18.2) | 3 [3] (8.8) |
| liver function test abnormal | | | 1 [1] (9.1) | 1 [1] (2.9) |
| nausea | | | 4 [3] (27.3) | 4 [3] (8.8) |
| neutrophil count decreased | 1 [1] (7.7) | 1 [1] (10.0) | | 2 [2] (5.9) |
| maculopapular rash | | | 1 [1] (9.1) | |
| urticaria | | | 1 [1] (9.1) | |
| vomiting | | | 1 [1] (9.1) | |

TEAE, treatment-emergent AE.
Data are presented as number of events [number of subjects] (%).
Events in subjects receiving placebo are not presented.

**Table 3.** PK parameters of LCB01-0371 at steady state after multiple administrations of LCB01-0371 for 21 days

| PK parameter[a] | 800 mg once daily ($n = 9$) | 800 mg twice daily ($n = 10$) | 1200 mg twice daily ($n = 9$) |
|---|---|---|---|
| $C_{max,ss}$ (ng/mL), mean±SD | 8931.3±4474.7 | 12647.2±6645.4 | 16287.8±6426.8 |
| $C_{min,ss}$ (ng/mL), mean±SD | 97.6±64.8 | 43.6±15.6 | 102.2±56.7 |
| $C_{av,ss}$ (ng/mL), mean±SD | 1672.3±526.7 | 1855±647.9 | 3511.5±961.1 |
| $T_{max,ss}$ (h), median (minimum, maximum) | 0.5 (0.5, 4) | 0.5 (0.5, 2) | 1 (1, 2) |
| $t_{1/2}$ (h), mean±SD | 1.7±0.4 | 1.5±0.1 | 1.5±0.1 |
| $AUC_{tau,ss}$ (ng·h/mL), mean±SD | 20067.7±6320.7 | 22259.8±7775.4 | 42137.4±11533.1 |
| $CL_{ss}/F$ (L/h), mean±SD | 44.1±18.3 | 39.9±14.2 | 30.1±7.5 |

$C_{av,ss}$, average concentration at steady state; $t_{1/2}$, terminal elimination $t_{1/2}$; $CL_{ss}/F$, CL/F at steady state.
[a]PK analysis was conducted in subjects who completed PK samplings.

The markedly high concentration detected in this subject should be investigated in further pharmacogenetic analysis. In total, compared with the number of ADRs in the 1200 mg twice-daily dose group, fewer than one-third occurred in the 800 mg once- or twice-daily dose groups. It can be suggested that the lower doses were safer and more tolerable than the higher dose due to low exposure to the drug in healthy male subjects.[14] There was no severe AE in this study.

PK profiles after 21 day multiple administrations of LCB01-0371 were evaluated and compared with previous results. The $C_{max,ss}$ for 800 and 1200 mg twice–daily doses were similar to those for the same doses in a previous study (14168.33±4685.34 and 20245.00±7148.88 ng/mL; K.-S. Bae, H. Nam and Y. L. Cho, unpublished data). $AUC_{tau,ss}$ values for the same doses were also consistent with the previous study (28080.07±7774.36 and 41117.12±12757.66 ng·h/mL). $C_{min,ss}$ was <1% of $C_{max,ss}$, indicating that accumulation after multiple administrations was minimal. This was also inferred from the accumulation ratio ($R$), calculated from the $k_{el}$ and dose interval [$R = 1/(1 - e^{-k_{el} \cdot tau}) = 1.004$].

High variability was observed in $C_{max,ss}$, with a coefficient of variability (CV) >40%. The $C_{max,ss}$ is commonly related to the absorption phase and its variability may be due to between-subject variability of the absorption processes. The $t_{1/2}$ values, however, showed a much smaller variability, the CV was <10% at the 800 and 1200 mg twice-daily doses. The $t_{1/2}$ of LCB01-0371 was relatively shorter than that of linezolid or tedizolid (4–6 and 12 h, respectively),[19,22] presumably due to high metabolic rate or renal excretion, and the rapid elimination process with little variability. Clearance of LCB01-0371 declined at high dose, as it did with

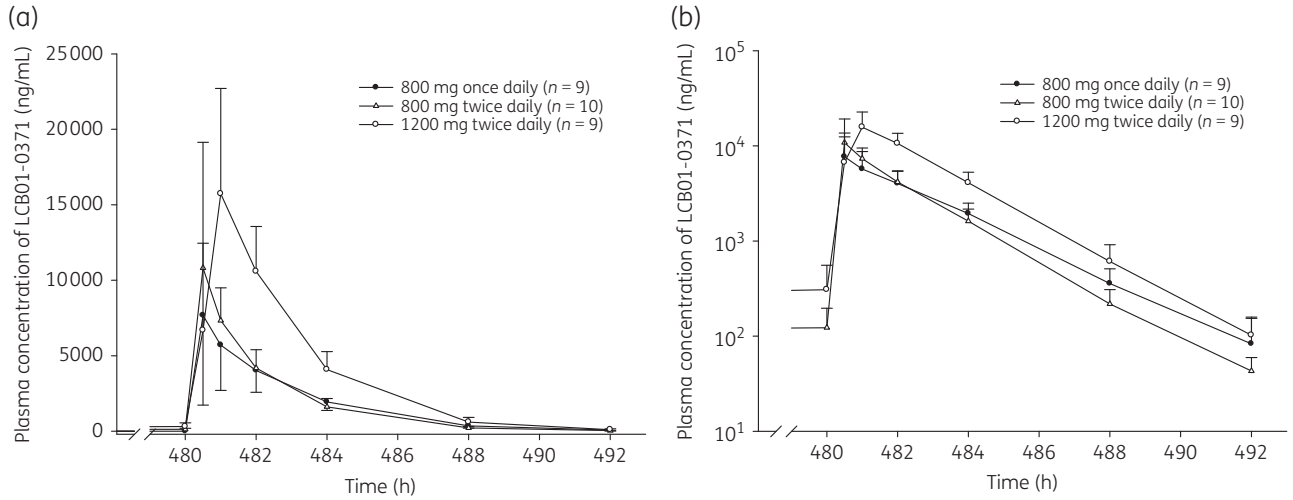


**Figure 3.** Concentration–time profile of LCB01-0371 at steady state on (a) linear and (b) semi-logarithmic scales, after multiple administrations of LCB01-0371 for 21 days.

linezolid.[12,23] As plasma protein binding of LCB01-0371 (37.1%) is similar to that of linezolid (37%), whose clearance is saturated at high dose levels,[12,19,23,24] clearance of LCB01-0371 might also be saturated in a similar manner. These PK characteristics could be applied in the determination of dosing regimens or in therapeutic drug monitoring for safe and effective treatment. As this study was primarily focused on evaluation of safety and tolerability, the PK profile was not intensively investigated. Further studies are ongoing to explore PK characteristics of LCB01-0371.

Our study has several limitations. First, reticulocyte count was not included in the haematological tests. Linezolid-induced reticulocytopenia is not common but is crucial, and it is recommended that it should be followed up because sometimes reticulocytopenia may not be associated with concurrent thrombocytopenia.[25] Second, the study subjects included only healthy male subjects aged 20–45 years. Paediatric, geriatric or female populations may be differently affected by LCB01-0371, as is the case for other oxazolidinones.[26] The narrow range of age and gender of study subjects limited the assessment of age and gender effects on safety and tolerability of LCB01-0371. Also, the results cannot be extrapolated to the patient population because this study was conducted only in healthy male volunteers. Patients who are being treated for long durations for multiple infections with decreased renal or hepatic functions are more vulnerable to the haematological AEs of the drug, although the haematological effect was minimal in healthy volunteers. The assessment and close monitoring of the safety and tolerability of LCB01-0371 and evaluation of its efficacy in patient populations are warranted.

In conclusion, the present study characterized the safety and tolerability of a novel oxazolidinone, LCB01-0371, in healthy male subjects. Despite two dropouts according to stopping rules, LCB01-0371 had comparable safety and haematology profiles to placebo in general after multiple doses of up to 1200 mg twice daily. Lower doses and lower exposures of LCB01-0371 caused fewer ADRs than higher doses. As the current study only included healthy male subjects, a larger clinical study in an expanded population with longer duration is necessary for determining the optimal drug regimen of LCB01-0371.

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## Transparency declarations

H. N. and Y. L. C. are employees of LegoChem BioSciences Inc. (Daejeon, Korea). All other authors: none to declare.

### *Author contributions*

H. N., Y. L. C. and J.-Y. C. were responsible for the conception of the original clinical trial. A. K., K. J. and J.-Y. C. were responsible for the design of the clinical trial including haematological safety analyses and PK analyses. A. K., K. J. and S. W. L. were responsible for conducting the clinical trial. Y. C. and S. W. L. were responsible for data analysis. Y. C., S. W. L., K.-S. Y., I.-J. J. and J.-Y. C. were involved in the interpretation of safety analyses and PK analyses. Y. C. was responsible for integrating data and creating first drafts. All authors critically reviewed and provided substantial input on all the manuscript drafts. All authors approved the final version of this manuscript for submission.

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