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ARTICLE

Safety, tolerability, pharmacokinetic/pharmacodynamic characteristics of bersiporocin, a novel prolyl-tRNA synthetase inhibitor, in healthy subjects

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Abstract

Bersiporocin, a novel first-in-class prolyl-tRNA synthetase (PRS) inhibitor currently under clinical development, was shown to exert an antifibrotic effect through the downregulation of collagen synthesis in various pulmonary fibrosis models. The aim of this first-in-human, randomized, double-blind, placebo-controlled, single- and multiple-dose, dose-escalation study was to evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of bersiporocin in healthy adults. A total of 40 and 32 subjects were included in a single- (SAD) and multiple-ascending dose (MAD) study, respectively. No severe or serious adverse events were observed after a single oral dose up to 600 mg and multiple oral doses up to 200 mg twice daily for 14 days. The most common treatment-emergent adverse events were gastrointestinal adverse events. To improve the tolerability, initial bersiporocin solution was changed to the enteric-coated formulation. Afterward, the enteric-coated tablet was used in the last cohort of SAD and in the MAD study. Bersiporocin showed dose-proportional PK characteristics after a single dose up to 600 mg and multiple doses up to 200 mg. Upon reviewing the safety and PK data, the final SAD cohort (800 mg enteric-coated tablet) was canceled by the Safety Review Committee. The levels of pro-peptide of type 3 procollagen were lower after treatment with bersiporocin than after the placebo in the MAD study, whereas no significant change was observed in other idiopathic pulmonary fibrosis (IPF) biomarkers. In conclusion, the safety, PK, and PD profile of bersiporocin supported its further investigation in patients with IPF.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Excessive deposition of collagen is a major pathological feature in idiopathic pulmonary fibrosis (IPF), and proline residues are the major constituents of collagen.

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Therefore, a prolyl-tRNA synthetase (PRS) inhibitor that downregulates collagen synthesis is expected to be a potential therapeutic agent against IPF.

WHAT QUESTION DID THIS STUDY ADDRESS?

What are the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic profiles of bersiporocin, a novel PRS inhibitor, in healthy subjects?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Bersiporocin showed a linear PK profile up to 600 mg as a single dose and 200 mg as a b.i.d. dose for 14 days in healthy adults. The area under the effect-time curve of pro-peptide of type 3 procollagen (Pro-C3), a potential biomarker of IPF, was lower after treatment with bersiporocin compared to the placebo.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Tolerable safety, linear PK characteristic, and potential of collagen downregulation of bersiporocin justify further investigation of this agent in patients with IPF.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive interstitial lung disease of unknown etiology, characterized by excessive accumulation of the extracellular matrix (ECM) in lung tissue, which is associated with proliferation and activation of fibroblasts, myofibroblasts, and abnormal lung epithelial cells.[1] Typical clinical manifestations of IPF include dyspnea, reduced exercise capacity, and dry cough.[2] Patients with IPF have a grave prognosis, and their median survival time is 3–5 years after the diagnosis.[3] Multiple factors among them, such as aging, genetic polymorphisms, and environmental factors including cigarette smoke exposure, can increase the risk of IPF.[4,5] If a genetically susceptible subject is chronically exposed to environmental risk factors, pathological changes may occur in the lung epithelium.[6–10]

Current pharmacologic treatments for IPF include two antifibrotic medications, nintedanib and pirfenidone, that appear to slow the disease progression, reduce the frequency of acute exacerbations, and produce some mortality benefit.[2,11–13] Nintedanib is a receptor blocker for multiple tyrosine kinases, which competitively blocks a plethora of fibrogenic growth factors involved in the pathogenesis of IPF, platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor.[14,15] The main benefits of nintedanib demonstrated in previous clinical trials were a reduced rate in the decline of lung function and a prolonged time to the first exacerbation of IPF.[15–20] The most commonly reported adverse effects of the drug include diarrhea (62%), not infrequently leading to dose reduction or discontinuation, nausea (24%), vomiting (12%), and elevation in liver function tests (14%).[15] Pirfenidone inhibits the synthesis of collagen induced by transforming growth factor beta, reduces ECM accumulation, and blocks fibroblast proliferation in vitro. In randomized clinical trials and case series, pirfenidone was shown to slow down the progression of IPF in patients with mild-to-moderate disease.[21–26] Moreover, a possible mortality benefit was demonstrated in an analysis of pooled data from three phase III trials and meta-analyses.[27,28] The most common side effects of pirfenidone include rash (30%) and an array of gastrointestinal events (13%–36%), in some cases, leading to drug reduction/interruption. Moreover, drug-induced liver disease may develop to the extent of serious or even fatal liver injury.[29] Unfortunately, the beneficial effects of the antifibrotic agents mentioned above are observed only in a subset of patients, and survival in those who responded to the treatment is not noticeably superior compared to the nonresponders. Other limiting factors of currently available therapies for IPF in terms of the clinical application are their common side effects and toxicity. All this warrants further research on more effective and less toxic treatment options for IPF.

Because the excessive deposition of the ECM is a pathological hallmark of fibrosis, blocking the de novo synthesis of collagen, a principal component of the ECM, is a potential therapeutic target in IPF. In previous in vitro and in vivo animal model studies for IPF, glutamyl-prolyl-tRNA-synthetase (PRS), an enzyme that conjugates proline to its RNA, regulates the expression of the ECM through the TGFβ1/STAT signaling pathway.[30] Additionally, the human PRS was significantly overexpressed in the lung tissues of patients with IPF.[31] Proline is one of the major constituents of collagen, which implies that PRS has an essential role in de novo collagen synthesis, suggesting to be a therapeutic target in IPF.

Bersiporocin (code name: DWN12088) is a novel first-in-class PRS inhibitor currently under clinical development by Daewoong Pharmaceutical . It is sparingly soluble in water (solubility of 19.55 mg/mL) and showed high permeability (apparent membrane permeability coefficient of $7.67 \pm 1.06 \times 10^{-6}$ cm/s) in in vitro Caco-2 cells.

It was expected to moderate proline synthesis by inhibiting PRS activity (Figure S1).[32] Previous nonclinical studies demonstrated the antifibrotic effect of bersiporocin associated with the downregulation of collagen synthesis in various cellular and mouse pulmonary fibrosis models. Bersiporocin reduced the synthesis of collagen and alpha-smooth muscle actin in patients with IPF derived primary lung fibroblasts stimulated with TGFβ. In the bleomycin-induced pulmonary fibrosis mouse model, the lung function measured by whole-body plethysmograph was considerably improved after oral administration of bersiporocin, and a significant reduction of collagen accumulation in the lung and heart tissues was observed.[31,33] The metabolite profile of bersiporocin was examined by liver microsomes and 21 metabolites were identified (Figure S2). Although M4 was found in the plasma of rats and M4, M9, and M12 in monkeys, major metabolites of bersiporocin in humans were M1, M8, M10, and M19, which were predominantly generated by CYP2D6. Among them, only M8 showed greater than 80% inhibition of PRS enzyme activity. Multiple-dose toxicity studies up to 28 days revealed no-observed-adverse-effect level (NOAEL) of 200 mg/kg/day in rats and 80 mg/kg/day in monkeys. Although vomiting was observed in monkeys, it was concluded not to be an adverse event (AE) because it was transient, and could possibly be due to the characteristics of the study drug, such as bitter taste.

Based on these understandings, the aim of this study was to evaluate the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) characteristics of bersiporocin in healthy adults.

METHODS

Study design and procedures

A first-in-human, randomized, double-blind, placebo-controlled, single- and multiple-dose, dose-escalation study was performed to evaluate the safety, tolerability, PKs, and PDs of bersiporocin in healthy subjects. The study was conducted in two parts in a consecutive order: single-ascending dose (SAD) study (part I) followed by a multiple-ascending dose (MAD) study (part II; Figure S3). Each subject was allowed in only one cohort, either in part I or Part II, but not in both parts of the study. Eligible subjects were randomized to either bersiporocin or placebo at a ratio of 6:2 in each dose group ($n = 8$, each). A sentinel dosing strategy was used in each cohort whereby the first two subjects (one to bersiporocin and the other to placebo) were initially randomized, dosed, and observed for 24 h before proceeding with further randomization of the remaining six. The dose escalation and expansion to the MAD study were based on the decision of the safety review committee (SRC), which consisted of the investigator, the sponsor representative, and two external independent experts.

The starting dose of bersiporocin (100 mg) in the SAD study was below the maximum recommended starting dose for a 60 kg adult, which was calculated as 154.8 mg based on a NOAEL in monkeys (safety factor = 10). The initial planned single dose levels of bersiporocin were between 100 and 1500 mg provided as a 150 mL solution. Nausea and vomiting were observed in five subjects (83.3%) in the starting dose group. Thus, to improve gastrointestinal tolerability, an enteric-coated capsule formulation was used for the SAD cohort 1b (100 mg), cohort 2 (300 mg), and cohort 3 (600 mg). Afterward, the study drug was once again reformulated to an enteric-coated tablet to avoid the dissolution of the capsules in the stomach. Based on the cumulative PK data and the predicted biologically active dose from bleomycin-induced pulmonary fibrosis mouse model, the targeted dose on the human area under the plasma concentration-time curve (AUC) was calculated to be 170 mg/day.[31,33] Consequently, the SRC recommended to cancel the 800 mg cohort after reviewing cumulative safety and PK data, and the 500 mg dose level (cohort 4) was the last SAD dose in tablet formation (Figure S3). In part II of the study, the tablet formulation of bersiporocin was administered twice daily (b.i.d.) for 14 days (morning dose only on day 14) at dose levels between 25 and 200 mg in four sequential cohorts (Figure S3).

On study days with intensive PK sample collections (day 1 for the SAD cohorts and the morning doses of day 1 and day 14 for the MAD cohorts), at least 10 h of overnight fasting was required prior to the dosing, and no food was allowed for at least 4 h postdose. For the rest of the doses in the MAD cohorts (i.e., the evening dose on day 1), and all doses administered on day 2 to day 13, the study drug was administered at least 1 h after the last meal, with no food or fluids allowed for at least 1.5 h after each dose. Subjects in the SAD cohort 1 were administered with a 150 mL solution (sweeting agent [Ora-Sweet] with diluted water) containing bersiporocin 100 mg, and immediately thereafter, the residues in the bottle were rinsed with 90 mL of water. Study drugs supplied as capsules (provided in a 100 or 200 mg strength) or tablets (provided in a 25 or 100 mg strength) were taken with 240 mL of water.

The safety and tolerability of bersiporocin were evaluated throughout the study periods. Serial blood and urine samples were collected to analyze the plasma and urine concentrations of bersiporocin and its metabolites (M1, M8, M10, and M19 for the MAD study only). In the MAD study, serum samples were collected to analyze biomarkers of collagen synthesis and turnover (Pro-C3,

Pro-C6, C3M, and C6M), which were known to correlate with the disease progression of IPF.[34,35] CYP2D6 genotyping was conducted in order to explore its possible impacts on PK characteristics on bersiporocin and the major metabolites.

Study subjects

This clinical study was conducted at the CMAX Clinical Research (Adelaide, Australia). Healthy male or female subjects, of any race, between 18 and 64 years old were eligible to participate in this study if they met the following criteria: body mass index between 18 and 30 kg/m^2, negative pregnancy test only for a woman of childbearing potential, and use of two effective contraceptive measures by a female subject or female partner of the male subject until 90 days after the last dosing unless the subject was a post-menopausal woman or surgically sterile woman or man. Key exclusion criteria were significant medical conditions, fasting blood glucose greater than 110 mg/dL, history of gastrointestinal surgery, including cholecystectomy, history of significant drug hypersensitivity, or positive test results to urine drug screening, alcohol breath test, human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C virus antibody. Written informed consent was obtained from all subjects before any study-related tests or procedures were carried out. Study procedures and study documents, including the consent form, were reviewed and approved by an institutional ethics committee (Bellberry Human Research Ethics Committee, Eastwood, Australia) before study initiation, and safety data were reviewed and approved by the ethics committee before progressing to the MAD study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the guideline for Good Clinical Practice, and applicable regulatory requirements. The study information is registered in the Australian New Zealand Clinical Trials Registry with the identifier ACTRN12619001239156.

Safety and tolerability

The safety and tolerability of bersiporocin were evaluated through the nature, incidence, severity, seriousness, and outcome of treatment-emergent adverse events (TEAEs). Adverse events were coded using the Medical Dictionary of Regulatory Activities (MedDRA) version 23.0. An adverse drug reaction (ADR) was defined as an AE for which the causality to bersiporocin could not be ruled out. Additionally, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, physical examinations, and 12-lead electrocardiograms were evaluated.

Determination of bersiporocin and its metabolite concentrations

In the SAD study, plasma samples were collected at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, and 72 h postdose. Urine was collected at 0–4, 4–8, 8–12, 12–24, 24–48, and 48–72 h postdose. In the MAD study, plasma samples were collected at predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h after the day 1 morning dose, at days 2, 3, 4, 7, 10, and 13 predoses, and at predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, and 72 h after the day 14 dose. Urine was collected at 0–4, 4–8, and 8–12 h after the day 1 morning dose and 0–4, 4–8, 8–12, 12–24, 24–48, and 48–72 h after the day 14 dose. Blood samples for CYP2D6 genotyping were collected at day 1. The plasma and urinary concentration of bersiporocin and the plasma concentration of the major metabolites of bersiporocin (M1, M8, M10, and M19) were determined by ultra-high-performance liquid chromatography tandem mass spectrometry using a 1290 Infinity II System (Agilent) and a 6460 Triple Quadrupole MS (Agilent). To prepare the samples for analysis, a sample of either plasma or urine was mixed with an internal standard (bersiporocin-d4; DAEWOONG Pharmaceutical). The mixture was then vortexed for 1 min and centrifuged for 10 min at 4°C and 2720 g. An aliquot of the supernatant (1 μL) was transferred to an autosampler onto the column at 35°C. The aqueous mobile phase consisted of 0.1% formic acid in water and 0.1% formic acid in acetonitrile. The precursor-to-product ion transition was detected by electrospray ionization with the multiple reaction monitoring mode (positive-ion mode). The precursor-to-product ion pairs of the mass-to-charge ratio were 328.1 to 142.1, 332.1 to 146.2, 520.1 to 142.1, 344.1 to 142.1, 504.1 to 142.1, and 342.1 to 156.1 for bersiporocin, bersiporocin-d4, M1, M8, M10, and M19, respectively. The calibration curves for bersiporocin and its metabolites were linear over the range of 2.5–1000 μg/L in the plasma samples and 2–800 μg/L in the urine samples. The limit of quantification (LLOQ) of bersiporocin and its metabolites in the plasma samples was 2.5 μg/L, and the LLOQ of bersiporocin in the urine samples was 2.0 μg/L.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed on the PK concentration data (plasma and urine), and the following PK parameters were calculated by noncompartmental analysis using the Phoenix WinNonlin software version 8.1

(Certara): maximum plasma drug concentration (C_{max}), maximum steady state plasma drug concentration during a dosage interval ($C_{max,ss}$), time to reach C_{max} (T_{max}), time to reach maximum plasma concentration following drug administration at steady state ($T_{max,ss}$), AUC during a dosage interval (τ) (AUCτ) on days 1 and 14, AUC from zero to time of last measurable concentration ($AUC_{0\text{-last}}$), AUC from zero to infinity ($AUC_{0\text{-}\infty}$), elimination half-life ($t_{1/2}$), apparent total clearance of the drug from the plasma after oral administration (CL/F), apparent volume of distribution during terminal phase after oral administration (Vz/F), mean residence time, parameters to assess renal drug clearance and drug excretion in urine, and metabolic ratio of metabolite(s) (MR). The MR was calculated based on $AUC_{0\text{-}\infty}$ of the metabolite(s) divided by $AUC_{0\text{-}\infty}$ of bersiporocin. The phenotypes of CYP2D6 were classified according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline and PK parameters were compared among different phenotypes.

Pharmacodynamic analysis

The serum samples were collected at predose, 2, 4, 6, and 12 h after the day 1 morning dose, at day 2 and day 7 predoses, and at predose, 2, 4, 6, 12, 24, 48, and 72 h after the day 14 dose in the MAD study. The serum concentration of the PD biomarkers (Pro-C3, Pro-C6, C3M, and C6M) was analyzed with validated enzyme-linked immunosorbent assay methods, the protocols which were published previously.[36–39] The area under the serum PD marker concentration-time curve during a dosage interval (AUECτ) and maximum percentage reduction over the PD marker on days 1 and 14 were calculated by noncompartmental analysis using the Phoenix WinNonlin software version 8.1.

Statistical analysis

The demographic characteristics of the subjects and the PK and PD parameters are presented as the arithmetic means and standard deviations (SDs). Dose linearity was evaluated with regression analysis on the natural log-transformed parameter values, using a power model with the following equations:

$$\ln(C_{max}) = \beta_0 + \beta_1 \times \ln(\text{Dose})$$

$$\ln(\text{AUC}) = \beta 0 + \beta 1 \times \ln(\text{Dose})$$

The point estimate of the slope (β_1) and its two-sided 90% confidence interval (CI) were calculated. If the 90% CI included 1, the PK parameters were evaluated as dose-proportional. To determine the time to steady-state, the mixed-effect ANOVA model with Helmert contrasts was used, for which log-transformed C_{trough} was set as an outcome variable, while the timepoint (day) was set as a fixed effect and a subject as a random effect. The time to steady-state was identified where the first Helmert contrast with $p > 0.05$ was achieved.[40] In this test, concentration at a specific timepoint is compared to the pooled concentration data, and the first timepoint in the last contrast is assumed to be the steady-state. A series of post hoc exploratory analyses was conducted to elucidate factors that might have affected gastrointestinal AEs, for example, subgroup analyses on the incidence of gastrointestinal disorders by sex, race, CYP2D6 metabolizer phenotype, the exposure level of bersiporocin or its metabolites, or dose timing (morning vs. evening, only for MAD cohorts). All statistical calculations were performed with SAS version 9.4 (Statistical Analysis Software Institute).

RESULTS

Subjects

In the SAD study, a total of 40 subjects were enrolled in five dose groups, including 30 receiving bersiporocin and 10 receiving placebo, and all the subjects completed the study as planned. In the MAD study, 32 subjects were enrolled in four dose groups, including 24 receiving bersiporocin and eight receiving placebo, and 29 of the 32 subjects completed the study as planned. One subject dropped out due to gastrointestinal ADRs while receiving bersiporocin 200 mg b.i.d., and two subjects withdrew their consent due to personal reasons (one receiving bersiporocin 50 mg b.i.d. and one receiving placebo). All subjects were included in the baseline data summary and safety analysis (SAD = 40, MAD = 32). All subjects exposed to bersiporocin were included in the PK and genotype analysis (SAD = 30, MAD = 24).

The demographic characteristics of the subjects were within the following ranges: 18 to 60 years (age) and 18.24 to 30.93 kg/m^2 (body mass index). The majority race of the subjects was White (85% in SAD and 66% in MAD) and more male subjects compared to female subjects were enrolled overall (70% in SAD and 75% in MAD). There were 18 different CYP2D6 genotype sets in the SAD study and 15 different genotype sets in the MAD study. The most common CYP2D6 phenotypes were normal metabolizers ($n = 16$ and $n = 10$ in the SAD and MAD studies, respectively) and intermediate metabolizers ($n = 13$ and $n = 11$ in the SAD and MAD studies, respectively). Three subjects had an ultrarapid metabolizer phenotype ($n = 1$ and $n = 2$

in the SAD and MAD studies, respectively), and one subject in the MAD study had a poor metabolizer phenotype. The demographics, baseline characteristics, and CYP2D6 phenotypes/diplotypes of the subjects are summarized in Table S1.

Safety and tolerability

During the SAD study, 90 TEAEs (68 ADRs) were reported in 23 subjects (77%) who received bersiporocin, and 16 TEAEs (3 ADRs) were reported in seven subjects (70%) in the placebo group (Tables 1 and 2 and Table S2). The incidence of ADRs was reduced after changing the bersiporocin formulation from solution to the capsule (12 events in 83% of subjects and 3 events in 50% of subjects in solution and capsule groups, respectively; Table 1). During the MAD study, 150 ADRs were reported in 21 subjects (88%) in the bersiporocin group, and 11 ADRs were reported in three subjects (38%) in the placebo group. Over the dose ranges analyzed in both parts of the study, the number of ADRs tended to increase with the higher doses (Tables 1 and 2). Most ADRs reported in subjects receiving bersiporocin across the study were mild in severity; gastrointestinal disorders were the most common ADRs. There were no severe, life-threatening, or fatal ADRs across the study.

No specific subgroup (i.e., sex, race, or CYP2D6 metabolizer phenotypes) indicated a higher incidence of gastrointestinal disorders from the post hoc analysis results. However, in the MAD study, those AEs occurred more frequently after the morning dose than after the evening dose. The number of events after morning dose versus evening dose was 134 versus 46 for overall TEAEs, 79 versus 27 for gastrointestinal TEAEs, 20 versus six for nausea, 12 versus four for diarrhea, 19 versus seven for abdominal pain, and nine versus zero for vomiting.

TABLE 1 Subject demographics summary of ADRs by preferred term in part I (SAD cohorts).

Preferred term	Bersiporocin 100 mg^{S} ($n = 6$)	Bersiporocin 100 mg^{C} ($n = 6$)	Bersiporocin 300 mg^{C} ($n = 6$)	Bersiporocin 600 mg^{C} ($n = 6$)	Bersiporocin 500 mg^{T} ($n = 6$)	Placebo ($n = 10$)
Subjects with ADRs	5 (83.3) [12]	3 (50.0) [3]	4 (66.7) [15]	5 (83.3) [15]	6 (100) [23]	3 (30.0) [3]
Nausea	5 (83.3) [5]	1 (16.7) [1]	3 (50.0) [4]	5 (83.3) [6]	5 (83.3) [5]	0
Vomiting	4 (66.7) [4]	0	3 (50.0) [3]	4 (66.7) [4]	2 (33.3) [2]	0
Diarrhea	0	0	2 (33.3) [2]	2 (33.3) [2]	4 (66.7) [4]	0
Abdominal pain	0	0	2 (33.3) [2]	0	1 (16.7) [1]	0
Constipation	0	0	0	0	1 (16.7) [1]	1 (10.0) [1]
Gastroesophageal reflux disease	0	1 (16.7) [1]	0	0	0	1 (10.0) [1]
Abdominal discomfort	0	0	0	1 (16.7) [1]	0	0
Abdominal distension	0	0	1 (16.7) [1]	0	0	0
Abdominal pain upper	0	0	0	0	1 (16.7) [1]	0
Epigastric discomfort	0	0	0	0	1 (16.7) [1]	0
Headache	2 (33.3) [2]	0	1 (16.7) [1]	1 (16.7) [1]	2 (33.3) [2]	0
Dysgeusia	1 (16.7) [1]	0	0	0	0	0
Neutropenia	0	1 (16.7) [1]	0	0	0	1 (10.0) [1]
Decreased appetite	0	0	1 (16.7) [1]	0	1 (16.7) [1]	0
Tachycardia	0	0	0	0	1 (16.7) [1]	0
Vertigo	0	0	0	0	1 (16.7) [1]	0
Malaise	0	0	1 (16.7) [1]	0	0	0
Hypersensitivity	0	0	0	0	1 (16.7) [1]	0
Oropharyngeal pain	0	0	0	0	1 (16.7) [1]	0
Photosensitivity reaction	0	0	0	1 (16.7) [1]	0	0
Hypotension	0	0	0	0	1 (16.7) [1]	0

Note: Data are displayed as the number of subjects (percentage of subjects) [number of events].

Abbreviations: ADR, adverse drug reaction; C, capsule; S, solution; SAD, single ascending dose; T, tablet.

TABLE 2 Summary of ADRs by preferred term in part II (MAD cohorts).

Preferred Term	Bersiporocin 25 mg^{T} ($n = 6$)	Bersiporocin 50 mg^{T} ($n = 6$)	Bersiporocin 100 mg^{T} ($n = 6$)	Bersiporocin 200 mg^{T} ($n = 6$)	Placebo ($n = 8$)
Subjects with ADRs	4 (66.7) [25]	6 (100) [35]	6 (100) [32]	5 (83.3) [58]	3 (37.5) [11]
Nausea	1 (16.7) [4]	4 (66.7) [6]	3 (50.0) [4]	5 (83.3) [12]	1 (12.5) [1]
Diarrhea	2 (33.3) [3]	2 (33.3) [2]	3 (50.0) [4]	4 (66.7) [7]	1 (12.5) [1]
Abdominal pain	2 (33.3) [5]	1 (16.7) [1]	3 (50.0) [8]	3 (50.0) [14]	0
Abdominal distension	2 (33.3) [3]	1 (16.7) [1]	2 (33.3) [3]	3 (50.0) [5]	0
Vomiting	0	3 (50.0) [5]	1 (16.7) [2]	2 (33.3) [2]	0
Abdominal pain upper	0	0	2 (33.3) [2]	0	1 (12.5) [1]
Constipation	0	1 (16.7) [1]	2 (33.3) [2]	0	0
Feces soft	0	0	2 (33.3) [2]	0	1 (12.5) [1]
Gastroesophageal reflux disease	1 (16.7) [2]	1 (16.7) [1]	0	0	1 (12.5) [1]
Salivary hypersecretion	2 (33.3) [3]	0	0	0	0
Abdominal discomfort	1 (16.7) [1]	0	0	0	0
Bowel movement irregularity	1 (16.7) [1]	0	0	0	0
Dry mouth	0	1 (16.7) [1]	0	0	0
Eructation	0	0	0	1 (16.7) [1]	0
Feces discolored	0	1 (16.7) [1]	0	0	0
Flatulence	0	0	0	1 (16.7) [1]	0
Esophageal pain	0	0	1 (16.7) [1]	0	0
Proctalgia	0	0	0	1 (16.7) [2]	0
Feeling hot	1 (16.7) [1]	0	0	0	0
Impaired healing	0	0	1 (16.7) [1]	0	0
Malaise	1 (16.7) [1]	0	0	0	0
Headache	0	3 (50.0) [5]	0	3 (50.0) [7]	2 (25.0) [2]
Dizziness	0	1 (16.7) [1]	0	2 (33.3) [2]	0
Dysgeusia	0	2 (33.3) [2]	0	0	0
Balance disorder	0	0	0	1 (16.7) [1]	0
Hypoesthesia	0	1 (16.7) [1]	0	0	0
Presyncope	0	0	1 (16.7) [1]	0	0
Somnolence	0	0	0	1 (16.7) [2]	
Tremor	0	0	0	1 (16.7) [1]	0
Papule	0	0	1 (16.7) [1]	0	1 (12.5) [1]
Skin irritation	0	0	1 (16.7) [1]	0	0
Acne	0	0	0	1 (16.7) [1]	0
Cold sweat	1 (16.7) [1]	0	0	0	0
Myalgia	0	2 (33.3) [2]	0	0	0
Alanine aminotransferase increased	0	1 (16.7) [1]	0	0	0
Transaminases increased	0	0	0	0	1 (12.5) [1]
Oropharyngeal pain	0	1 (16.7) [1]	0	0	0
Pollakiuria	0	1 (16.7) [1]	0	0	0
Neutropenia	0	0	0	0	1 (12.5) [1]
Altered visual depth perception	0	1 (16.7) [1]	0	0	0
Decreased appetite	0	0	0	0	1 (12.5) [1]
Euphoric mood	0	1 (16.7) [1]	0	0	0

Note: Data are displayed as the number of subjects (percentage of subjects) [number of events].

Abbreviations: ADR, adverse drug reaction; MAD, multiple ascending dose; T, tablet.

Three abnormal physical examination findings (puffy eyes, epigastric voluntary guarding, and mild pigment on the left cubital fossa) turned out to be associated with TEAEs (hypersensitivity, abdominal pain, and catheter site-related reaction, respectively). No other clinically significant abnormalities were found in the physical examinations, vital signs, 12-lead electrocardiograms, or safety laboratory parameters.

Pharmacokinetics

After the administration of a single dose of the oral bersiporocin enteric coated capsule, the plasma concentration of bersiporocin increased in a dose-proportional manner (Figure 1 and Figure S4). The 90% CI of the slope of the power model included 1.0 (0.36–1.09 [slope estimate; 0.72] and 0.65–1.25 [slope estimate; 0.95], for C_{max} and $AUC_{0-\infty}$, respectively). The Vz/F, CL/F, and $t_{1/2}$ after the multiple dose did not show any dose-dependent increment or decrement, and considerable PK variability was observed (Table 3). The plasma concentration of bersiporocin reached a C_{max} in the range of 1.50 to 8.00 h postdose and showed a multicompartmental elimination profile (Figure 1) with a $t_{1/2}$ of ~6.91 to 9.90 h (Table 3). Comparing the PK parameters after a single dose of bersiporocin 100 mg, the T_{max} was prolonged in both enteric coated formulations and the bioavailability was greatest in enteric coated capsules.

After multiple administrations of the bersiporocin enteric coated tablet in the MAD study, the plasma concentration of bersiporocin reached a steady-state on day 2 and accumulated 1.88 to 3.75-fold by repeated drug administrations (Figure 2 and Table 4). The first Helmert contrast with a $p > 0.05$ was observed on day 2. The plasma concentration of bersiporocin increased in a dose-proportional manner after single and multiple doses (Figure 2 and Figure S4 and Table 4). The 90% CI of the slope of the power model included 1.0 (0.79–1.26 [slope estimate; 1.02], 0.75–1.24 [slope estimate; 0.99], and 0.89–1.64 [slope estimate, 1.25] for C_{max}, $AUC_{0\text{-last}}$, and $AUC\tau$, respectively). However, AUC of bersiporocin increased more than four-folds in the 100 to 200 mg dose group. The Vz/F, CL/F, and $t_{1/2}$ did not exhibit any dose-dependent increment or decrement, however, CL/F decreased at the day 14 dose compared to the one at the first dose (Table 4). The median $T_{max,ss}$ ranged from 2.0 to 6.0 h and was similar after a single dose (2.5–6 h). The $t_{1/2}$ was prolonged after multiple doses compared to the one after a single dose (Tables 3 and 4). The dose adjusted plasma exposure of bersiporocin was six- to nine-fold higher in the CYP2D6 poor metabolizer compared to the median value in other phenotypes (Figure S4). Urine PK data, either from the SAD or MAD, indicated that renal elimination was not the major clearance pathway for bersiporocin (Tables 3 and 4). Four bersiporocin metabolites (M1, M8, M10, and M19) were identified in the plasma, and the plasma exposure of M1 and M8 was higher than those of other metabolites (Table 4). The mean metabolite to parent (bersiporocin) ratio ranged from 2.72 to 14.59 and from 2.45 to 10.93 for M1 and M8, respectively (Table 4). The metabolic ratio showed the tendency to decrease as the dose increased. No significant differences in the dose-normalized C_{max} or AUCs of bersiporocin were observed among the different

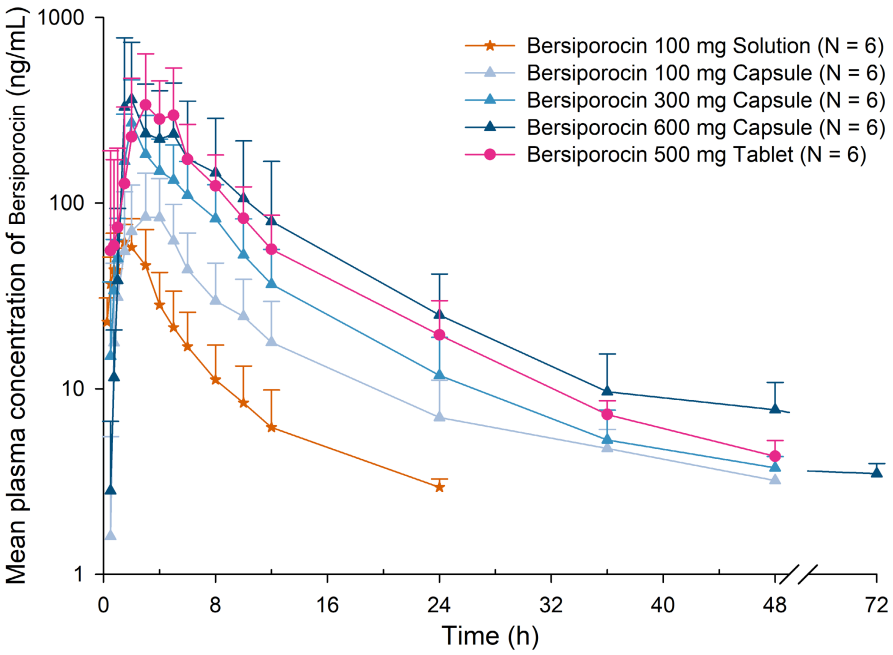


FIGURE 1 Mean plasma concentration-time profiles of bersiporocin after single administration in part I (semi-logarithmic scale). Error bars the denote standard deviation.

TABLE 3 PK parameters of bersiporocin after single oral administration in part I (SAD cohorts).

PK parameter	Bersiporocin 100 mg[S] (*n* = 6)	Bersiporocin 100 mg[C] (*n* = 6)	Bersiporocin 300 mg[C] (*n* = 6)	Bersiporocin 600 mg[C] (*n* = 6)	Bersiporocin 500 mg[T] (*n* = 6)
C_{max}, ng/mL	72.33 (29.35)	123.96 (37.72)	276.80 (66.21)	213.43 (433.75)	513.56 (41.27)
T_{max}, h	1.79 (0.75,2.00)	3.00 (1.50,4.00)	2.50 (1.50,8.00)	2.00 (1.50,5.00)	3.01 (0.50,5.00)
$AUC_{0\text{-last}}$, h•ng/mL	274.62 (49.65)	594.10 (61.23)	1478.84 (48.07)	1008.65 (625.00)	2282.37 (54.92)
$AUC_{0\text{-}\infty}$, h•ng/mL	293.50 (48.72)	639.07 (58.10)	1525.99 (47.06)	1922.64 (222.08)	2339.20 (53.27)
$t_{1/2}$, h	3.84 (43.55)	6.91 (39.98)	8.33 (24.57)	9.90 (71.50)	7.80 (13.49)
V_Z/F, L	1885.66 (8.30)	1560.44 (34.98)	2361.87 (41.96)	4459.07 (84.14)	2406.62 (48.04)
CL/F, L/h	340.72 (48.72)	156.48 (58.10)	196.59 (47.06)	312.07 (222.08)	213.75 (53.27)
MRT, h	5.17 (30.77)	9.26 (33.69)	9.75 (21.76)	9.79 (25.60)	9.57 (27.28)
$Fe_{0\text{-}72h}$, %	7.59 (32.47)	10.01 (45.08)	7.42 (43.31)	3.09 (341.55)	42.18 (180.78)
$CLr_{0\text{-}72h}$, L/h	25.87 (30.20)	15.71 (31.24)	14.64 (25.51)	16.56 (22.34)	90.39 (101.46)

Note: Data are presented as the geometric mean (geometric coefficient of variation%), except for T_{max}, which is represented as the median (minimum and maximum).

Abbreviations: $AUC_{0\text{-last}}$, area under the plasma concentration-time curve from 0 to the time of the last measured concentration; $AUC_{0\text{-}\infty}$, AUC from time of dosing extrapolated to infinity; C, capsule; CL/F, apparent total clearance; $CLr_{0\text{-}72h}$, renal clearance from zero to 72 hours; C_{max}, maximum plasma concentration; $Fe_{0\text{-}72h}$, fraction excreted in urine from zero to 72 hours; MRT, mean residence time; PK, pharmacokinetic; S, solution; SAD, single ascending dose; $t_{1/2}$, elimination half-life; T, tablet; T_{max}, time to reach maximum plasma concentration; Vz/F, apparent volume of distribution.

CYP2D6 phenotype subjects (Figure S5). However, the dose adjusted plasma exposure of bersiporocin was six- to nine-fold higher in the CYP2D6 poor metabolizer compared to the median value in other phenotypes.

Pharmacodynamics

In the MAD study, the mean $AUEC_{0\text{-}12h}$ value for serum Pro-C3 was lower in the bersiporocin-treated groups compared to the placebo-treated group (Figure 3 and Table S3). The differences were statistically significant after a single dose but not after multiple doses (Figure 3). No apparent trend or significant differences between the bersiporocin-treated groups and the placebo-treated group were observed in the other PD parameters (Table S3).

DISCUSSION

This first-in-human phase I study elucidated that bersiporocin, a first-in-class PRS inhibitor, was generally safe in healthy male and female subjects. No severe or serious AEs were observed after a single dose up to 600 mg and multiple doses up to 200 mg. The most common TEAEs observed in the study subjects were gastrointestinal AEs, such as nausea, diarrhea, abdominal pain, and vomiting, where most of them were mild and resolved spontaneously.

In this study, a diurnal variation in the frequency of TEAEs was observed. The TEAEs in the MAD study, including common gastrointestinal TEAEs, occurred more than twice as often after the morning dose than after the evening dose. The number of events for nausea, diarrhea, abdominal pain, and vomiting after the morning dose was 20, 12, 19, and nine, respectively, compared to six, four, seven, and zero, respectively, after the evening dose. In the MAD study, the morning doses were administered in a fasted state (after at least 10 h of overnight fasting), whereas the evening doses were administered about 1.5 h after a meal. Because the current study was not designed to analyze the effects of food on the PK and tolerability of bersiporocin, it was unclear if this phenomenon was diet-related. The effect of food on the PKs and tolerability of bersiporocin will be addressed in the following clinical study (ClinicalTrials.gov Identifier: NCT04767815). In addition, when a subgroup analysis was performed excluding subjects in the SAD study with little exposure (i.e., $AUC_{0\text{-last}}$ <1.5 interquartile range of treatment group) from the PK set, no subjects were excluded. This implies that gastrointestinal TEAEs, such as vomiting, had little impact on the exposure of bersiporocin. Considering that

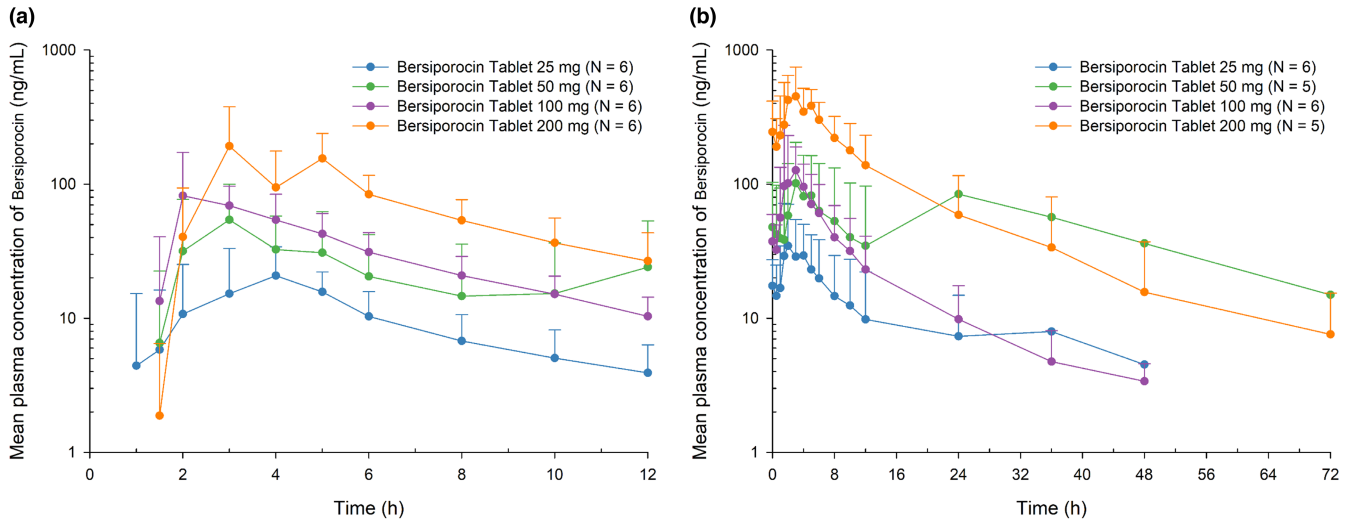


FIGURE 2 Mean plasma concentration-time profiles of bersiporocin after (a) single and (b) multiple administration in part II (semi-logarithmic scale). Error bars denote the standard deviation.

enteric-coated tablets were used in the MAD study, which were shown to be more tolerable than other formulations, we consider that the impact of gastrointestinal TEAES on the PK evaluations would also be negligible in the MAD study.

Bersiporocin demonstrated dose-proportional PK characteristics after a single dose up to 600 mg and multiple doses up to 200 mg. Although the deviation from dose proportionality did not reach statistical significance, the increase in exposure appeared to be more than dose proportional in the 100 to 200 mg b.i.d. dose range, indicating the potential for nonlinear PK characteristics in the higher doses. Urinary excretion was not the major elimination pathway of bersiporocin (Tables 3 and 4). The major route of elimination of bersiporocin was phase I and phase II metabolism mediated by various liver enzymes, such as CYP2C19, CYP2D6, CYP3A4, UGT2B4, and UGT2B7; bersiporocin did not inhibit those CYP and UGT enzymes at therapeutic concentration ranges (data on file). Although the $t_{1/2}$ of bersiporocin increased after multiple doses, large interindividual variability made it difficult to conclude the drug–drug interaction (DDI) liabilities of bersiporocin and its major metabolites. More studies exploring the DDI potential of bersiporocin with substrates of various liver enzymes might be necessary. The *V*z/F and CL/F also showed high interindividual variability, and CYP2D6 genetic variability would be one of the reasons behind this phenomenon (Tables 3 and 4). The AUCs for M1 and M8 were 2.4- to 14.6-fold higher than that of bersiporocin (Table 4). Considering that M8 inhibits PRS enzyme activity as much as bersiporocin, its clinical significance needs to be elucidated in future studies. Moreover, the metabolic ratio tended to decrease in higher doses after multiple doses. This could be explained by the combination of an increase in AUC of bersiporocin more and increase in AUC of metabolites less than dose-proportional manner. Regarding that bersiporocin is metabolized by CYP2D6, it might have the potential for auto-inhibition after multiple doses.

The pro-peptide of type 3 procollagen (Pro-C3) levels were lower after treatment with the bersiporocin than after treatment with the placebo in the MAD study, but no clear dose–response relationship was observed (Figure 3 and Table S3). Type 3 collagen was commonly accumulated in the fibrotic lung and liver tissues, and the serum concentration of Pro-C3, a fragment of type 3 collagen, was suggested as a potential biomarker of IPF in previous studies.[41–43] One of the mechanisms of bersiporocin action was the inhibition of collagen synthesis, and, hence, a decrease in the serum Pro-C3 levels was anticipated in patients with IPF treated with bersiporocin.[44] Low serum Pro-C3 levels found in bersiporocin-treated subjects implied that type 3 collagen synthesis could be downregulated in healthy subjects by bersiporocin treatment, and, thus, this agent was also likely to show an antifibrotic activity in patients with IPF. Considering the safety and PD results, more than a 100 mg dose of bersiporocin twice daily were considered to be a therapeutic dose for further clinical studies in patients with IPF.

There were some limitations in this study. First, because this study was conducted with a relatively small number of healthy subjects, the occurrence of gastrointestinal AEs in some of the more susceptible subjects may have contributed to a high overall frequency of AEs in some dose groups. As this study was the

TABLE 4 PK parameters of bersiporocin after single and multiple oral administration in part II (MAD cohorts).

	PK parameter	Bersiporocin 25 mg^T ($n = 6$)	Bersiporocin 50 mg^T ($n = 6$)	Bersiporocin 100 mg^T ($n = 6$)	Bersiporocin 200 mg^T ($n = 6$)
Single administration (day 1)	C_{max}, ng/mL	26.65 (44.86)	69.99 (65.24)	95.73 (64.85)	255.60 (47.32)
	T_{max}, h	3.50 (3.00, 5.00)	3.00 (2.00, 5.00)	2.50 (2.00, 4.00)	3.00 (3.00, 5.05)
	AUCτ	94.26 (50.81)	214.70 (73.60)	328.53 (51.18)	740.64 (38.93)
	$t_{1/2}$, h	4.20 (12.83)	2.95 (88.49)	3.81 (9.49)	3.74 (21.49)
	V_Z/F, L	1040.49 (64.69)	901.92 (44.00)	1439.37 (49.89)	1341.67 (12.89)
	CL/F, L/h	175.57 (70.55)	292.89 (26.44)	261.98 (49.54)	266.78 (18.62)
	MRT, h	7.36 (6.72)	4.70 (23.30)	6.84 (10.04)	7.20 (15.61)
	$Fe_{0\text{-}12h}$, %	6.23 (44.75)	6.09 (95.30)	8.20 (27.21)	8.44 (50.39)
	$CLr_{0\text{-}12h}$, L/h	16.52 (22.24)	15.21 (71.94)	24.95 (31.95)	22.79 (28.26)
Multiple administration (day 14)	$C_{max\ ss}$, ng/mL	36.50 (66.19)	102.61 (67.99)	151.27 (65.36)	595.35 (36.32)
	$T_{max\ ss}$, h	2.00 (1.50, 4.00)	3.00 (3.00, 5.00)	3.00 (1.50, 4.00)	2.00 (1.50, 5.00)
	AUCτ	183.32 (76.35)	429.09 (128.63)	617.40 (60.53)	3012.35 (48.42)
	$t_{1/2}$, h	7.63 (46.84)	4.40 (101.38)	9.26 (22.69)	12.35 (34.54)
	V_Z/F_{ss}, L	1433.79 (61.75)	738.97 (34.90)	2163.04 (63.58)	1182.53 (48.47)
	CL/F_{ss}, L/h	122.65 (79.49)	116.53 (128.63)	161.97 (60.53)	66.39 (48.42)
	MRT, h	10.53 (31.65)	8.44 (68.43)	10.17 (9.35)	12.07 (26.90)
	Accumulation ratio[a]	1.94 (26.34)	2.33 (31.42)	1.88 (35.07)	3.75 (36.01)
	$Fe_{0\text{-}12h}$, %	6.23 (44.75)	6.09 (95.30)	8.20 (27.21)	8.44 (50.39)
	$CLr_{0\text{-}12h}$, L/h	16.52 (22.24)	15.21 (71.94)	24.95 (31.95)	22.79 (28.26)
	M1 MR[b]	11.99 (5.98)	14.59 (6.06)	5.95 (2.18)	2.72 (1.50)
	M8 MR[b]	8.76 (5.13)	10.93 (4.52)	5.00 (1.70)	2.45 (0.56)
	M10 MR[b]	0.79	0.99 (0.25)	0.39 (0.07)	0.85 (0.17)
	M19 MR[b]	3.22 (1.6)	3.90 (0.98)	1.74 (0.73)	0.78 (0.50)

Note: Data are presented as the geometric mean (geometric coefficient of variation%), except for T_{max} and $T_{max,ss}$, which are represented as the median (min, max).

Abbreviations: AUCτ, AUC within a dosing interval; C, capsule; C_{max}, maximum plasma concentration; $C_{max,ss}$, maximum plasma concentration at steady state; CL/F, apparent total clearance; CL/F_{ss}, apparent total clearance at steady state; $CLr_{0\text{-}12h}$, renal clearance from zero to 12 hours; $Fe_{0\text{-}12h}$, fraction excreted in urine from zero to 12 hours; MAD, multiple ascending dose; MR, metabolic ratio; MRT, mean residence time; PK, pharmacokinetic; S, solution; $t_{1/2}$, elimination half-life; T, tablet; T_{max}, time to reach maximum plasma concentration; $T_{max,ss}$, time to reach maximum plasma concentration at steady state; Vz/F, apparent volume of distribution; Vz/F_{ss}, apparent volume of distribution at steady state.

[a]Accumulation ratio was calculated based on AUCτ.

[b]MR was calculated based on $AUC_{0\text{-}\infty}$ of metabolite/$AUC_{0\text{-}\infty}$ of bersiporocin.

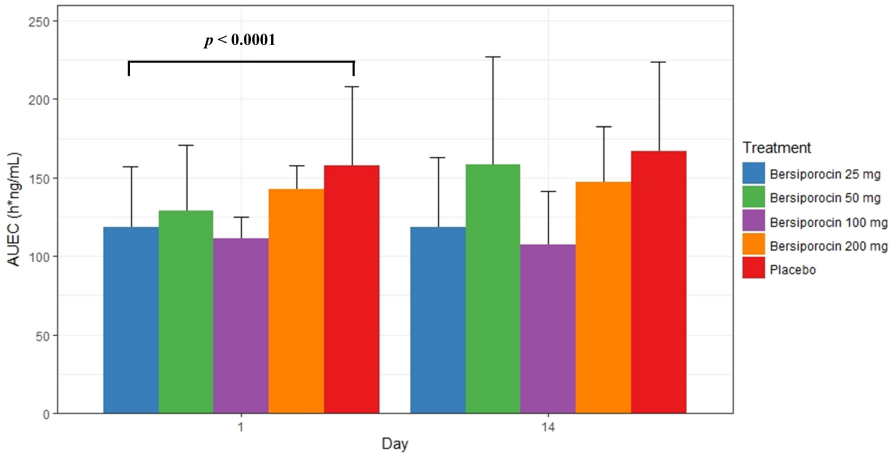


FIGURE 3 Comparison of area under the effect-time curve (AUEC) of Pro-C3 according to treatment groups in part II. Error bars denote the standard deviation.

first-in-human trial of bersiporocin, the PK characteristics of bersiporocin was evaluated in the fasted state to exclude confounding effects of food. However, considering gastrointestinal TEAEs occurred more often in the morning period compared to the evening period, administration of bersiporocin with food might improve its tolerability. Moreover, as most of the gastrointestinal AEs were mild in severity, the tolerability of bersiporocin might be enhanced by other medications, such as antiemetics, which needs to be further investigated in future clinical studies. Second, no clear dose–response relationship was observed in the PD biomarkers. Healthy subjects generally had lower serum biomarker levels than patients with IPF, and interindividual variability in the PD biomarker levels may have constituted a reason behind the lack of any clear dose–response relationship observed in this study.[34,35]

In conclusion, the safety profile of bersiporocin, and its PK and PD profile supported further investigation of this agent in patients with IPF.

AUTHOR CONTRIBUTIONS

M.Y.P., S.B., I.J.J., K.S.Y., and J.O. wrote the manuscript. M.Y.P., Y.K., and J.H. designed the research. M.Y.P., J.H., and M.P. performed the research. M.Y.P., J.H., S.B., and J.O. analyzed the data. M.Y.P. and Y.K. contributed new reagents/analytical tools.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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