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ARTICLE

The bioequivalence of fixed-dose combination tablets of bisoprolol and ramipril and its drug-drug interaction potential

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Abstract

Chronic antihypertensive treatment often includes combination of two or more therapies with complementary mechanism of action targeting different blood pressure (BP) control system. If available, these components are recommended to be administered as a fixed-dose combination (FDC) to reduce tablet burden, improve adherence and thus BP control. A combination of ramipril (RAMI) and bisoprolol (BISO) is one of the options used in clinical practice and is supported by therapeutic guidelines. The clinical program for a novel BISO/RAMI FDC consisted of two randomized, open-label, bioequivalence (BE) studies and one drug-drug interaction (DDI) study. The BE was examined between two FDC strengths of BISO/RAMI (10/10 and 10/5 mg) and the individual reference products administered concomitantly at respective doses after a single oral dose under fasting conditions. In both BE studies, 64 healthy subjects were randomized according to a two-way crossover design. The DDI study evaluated a potential pharmacokinetic (PK) interaction between BISO 10 mg and RAMI 10 mg following their single or concomitant administrations in 30 healthy subjects under fasting condition. BE for BISO/RAMI 10/5 mg and absence of a clinically relevant PK DDI between BISO and RAMI was demonstrated as the 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) for area under the concentration time curve (AUC) and maximum concentration (C_{max}) remained within the acceptance range of 80.00 to 125.00%. However, BE for BISO/RAMI 10/10 mg was not demonstrated, as the lower bound of the 90% CI of C_{max} for RAMI was outside the acceptance range of BE. Both drugs administered alone or combined were well-tolerated. No PK interaction was observed between BISO and RAMI/ramiprilat, since the co-administration of BISO and RAMI 10 mg single doses resulted in comparable rate and extent of absorption for BISO and RAMI when compared to their individual products.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Bisoprolol (BISO) and ramipril (RAMI) have both well-characterized pharmacokinetic (PK) properties, however, clinical studies for this fixed-dose combination (FDC) are limited and as per our knowledge, a potential of PK drug-drug interactions (DDIs) between both compounds has not been evaluated.

WHAT QUESTION DID THIS STUDY ADDRESS?

The clinical program was focused on the evaluation of bioequivalence (BE) for two strengths of novel FDCs containing BISO/RAMI in comparison with their free-combinations and evaluation of potential PK interaction between BISO and RAMI.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

An absence of PK interaction between BISO and RAMI has been demonstrated in the DDI study. The BE studies provided information about in vivo behavior of the FDC, as well as additional PK, and statistical and safety data for BISO and RAMI.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

FDC containing BISO and RAMI may reduce tablet burden, improve adherence to treatment, and blood pressure control in patients with hypertension. The administration of BISO and RAMI is not associated with a risk of PK interaction between both compounds.

INTRODUCTION

Elevated blood pressure (BP), or hypertension, is one of the leading risk factor accounting for 10.8 million of death worldwide in 2019 with more than 1.3 billion people diagnosed (data from 2010).[1,2] In addition, effective BP management is achieved in less than one in five patients with antihypertension.[3] Chronic antihypertensive treatment often includes a combination of two or more therapies with complementary mechanism of action targeting different BP control system.[4-6] As per therapeutic recommendations published in 2018, antihypertensive treatment should be initiated with a two-drug combination, preferably in a fixed-dose combination (FDC).[5] The additive antihypertensive effect by combining angiotensin converting enzyme inhibitor (ACEI) with a calcium channel blocker (CCB) or with thiazide or thiazide-like diuretics, or combining angiotensin receptor blocker (ARB) with either CCB or thiazide or thiazide-like diuretics have been recently recommended.[7] In addition, combinations with beta (β)-blockers (BBs) have a growing body of clinical evidence of improved efficacy in the treatment of uncontrolled hypertension.[8-18] A retrospective analysis showed that the combination of BBs with ACEI was equivalent to BBs combined with CCB and superior to BBs combined with ARB in reducing systolic BP, whereas diastolic BP significantly decreased when BBs were combined with CCBs, although it was decreased similarly when combined with ARBs.[16] BBs in combination are specifically recommended for patients with hypertension with certain comorbidities, such as symptomatic angina, post-myocardial infarction, or chronic mild to moderate heart failure with reduced ejection fraction, for patients requiring heart rate control and as an alternative to ACEI or ARB in younger women with hypertension planning pregnancy or of child-bearing potential.[5]

Bisoprolol (BISO), a second-generation of long-acting BBs predominantly selective for β_1-adrenoreceptors, and ramipril (RAMI), an ACEI, are both indicated in the treatment and management of hypertension and routinely prescribed at different dose combinations as recommended in hypertension, coronary artery disease, and mild to moderate heart failure guidelines.[19-21] The availability of FDCs (two or more active substances formulated into one single dosage form) to manage hypertension is limited despite evidence of improved adherence when compared with drugs administered separately (free-combination) and therapeutic recommendations.[5,6,7,22,23,24] The analysis of co-prescription data from Germany identified a substantial number of patients treated with BISO and RAMI in free-combination as shown in this manuscript. As such, an FDC of BISO and RAMI in four different strengths (10/10, 10/5, 5/10, and 5/5 mg) was developed to cover the therapeutic scenario of substitution in patients with arterial hypertension adequately controlled with BISO and RAMI used in free-combination and provide additional

treatment option for patients, which are suitable for initial combination treatment with BBs and ACEI.

The clinical program of BISO/RAMI FDC consisted of two bioequivalence (BE) studies that evaluated bioavailability of two strengths of BISO/RAMI FDCs (10/10 mg and 10/5 mg) in comparison with their free-combinations and one study that investigated the potential for drug-drug interaction (DDI) at the highest dose level (BISO 10 mg + RAMI 10 mg administered concomitantly vs. individual products administered separately). BE studies for the remaining strengths (5/10 and 5/5 mg) may be waived, as the products both fulfill general biowaiver criteria with regard to manufacturing process, qualitative and quantitative composition, in vitro dissolution, and, at the same time, BISO and RAMI both exhibit linear PK.[25-29]

METHODS

The protocols and informed consent forms for three clinical studies were reviewed and approved by Health Canada and by Institutional Review Board Advarra (Canada). These studies were conducted between January 2019 and February 2020 at Altasciences, Montreal, Canada, in compliance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki, the International Council for Harmonisation (ICH), Good Clinical Practice, and applicable regulatory requirements. All subjects gave informed consent prior to study participation.

Study treatments and design

Study 1 and study 2 assessed the BE between the tested FDC of BISO/RAMI (10/10 and 10/5 mg in studies 1 and 2, respectively) and co-administered individual reference products of BISO + RAMI in respective doses under fasting conditions in healthy volunteers. Both studies were single center, randomized, open-label, laboratory-blinded, two-treatment, two-period, two-sequence, single dose crossover studies. Both test formulations were manufactured by Sanofi – Synthelabo, India and Zentiva, k.s., Czech Republic in Good Manufacturing Practice (GMP) facilities. The individual reference products Concor 10 mg film-coated tablets (Merck Serono GmbH, Germany) containing BISO fumarate, Delix Protect 10 mg tablets and Delix 5 mg tablets (Sanofi-Aventis Deutschland GmbH, Germany) containing RAMI were purchased from the German market.

Study 3 assessed the potential of PK interaction between BISO and RAMI following the co-administration of both drugs versus the administration of each drug alone after a single oral dose under fasting conditions in healthy volunteers. It was a single center, randomized, single dose, open-label, three-treatment, three-period, six-sequence, crossover study. Only the reference products were Concor 10 mg film-coated tablets, (Merck Serono GmbH, Germany) and Delix Protect 10 mg tablets (Sanofi-Aventis Deutschland GmbH, Germany) purchased from the German market were administered in study 3. Treatments were administered to subjects in a randomized fashion (Table 2).

The evaluation of BE and pharmacokinetic (PK) interaction was based upon plasma concentrations of the parent compounds (BISO and RAMI). Ramiprilat, the active metabolite of RAMI, was measured in all three studies for information purposes.

A washout period of at least 21 days was kept between treatment administrations in consideration of ramiprilat half-life (13–17 h).[29] Fasting conditions were considered as the most sensitive to detect a potential difference between formulations and to assess a potential interaction between both compounds. As BISO and RAMI may be administered without regard to meal and do not display a significant food effect, all three studies were conducted under fasting conditions.[28,29] During each period, subjects arrived at the clinical site at least 10 h before treatment administration and were housed for 36-h postdose. Subjects returned to the clinical site for the two remaining blood samples at 48 and 72 h postdose. The treatments were received according to randomization code generated by SAS (version 9.4). Each treatment was administered in the morning after a 10-h supervised overnight fasting. Water was freely available to the subjects, however, it was restricted within 1 h before and 1 h after the administration of the drug. An oral dose of the assigned treatment was administered to subjects with ~ 240 ml of water at ambient temperature. The tablet(s) had to be swallowed whole, chewing or crushing was forbidden. Fasting continued for at least 4 h following treatment administration, after which a standardized lunch was served. A supper, a light snack, and other meals were then served at appropriate times.

Subjects

Subject eligibility was determined based on medical history, physical examination, vital signs, electrocardiogram (ECG), and laboratory screening tests. Healthy adult non-smoking male and female volunteers, aged 18 to 50 years (study 1 and study 2) and to 60 years (study 3) with a body mass index (BMI) between 18 and 30 kg/m^2 (inclusively) were eligible to participate in these studies. Female subjects were required to be of non-childbearing potential.

Subjects were ineligible if they had seated pulse rate less than 60 beats per minute or seated blood pressure below

105/60 mmHg, documented hypersensitivity to any of the study medications, positive screening human immunodeficiency virus Ag/Ab Combo, hepatitis B surface antigen or hepatitis C virus test result, history or presence of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic, gastrointestinal, liver, or kidney disease. Pregnant or lactating women were not eligible. Subjects could not have participated in a clinical trial if they received any BISO or RAMI products or having donated 50 ml or more of blood within 28 days prior to the first dosing.

Use of prescription and nonprescription drugs (including vitamins or herbal and dietary supplements) was precluded within 28 and 7 days prior to the first dose of study medication, respectively. Food or beverages containing xanthines, grapefruit, and/or pomelo were restricted 48 h prior to study drug administration. Alcohol consumption was not allowed for 48 h prior to each dosing and during each study period. Subjects underwent alcohol and drugs of abuse tests at screening and prior to each study period. Subjects had screening visits within 28 days prior to the first dose of the study drug.

PK sample collection

Blood samples were collected in vacutainers containing K_2EDTA as anticoagulant predose and up to 48 and 72 h after dosing of BISO and RAMI, respectively. Blood samples for evaluation of BISO were collected predose and at 0.50, 0.83, 1.00, 1.33, 1.67, 2.00, 2.33, 2.50, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, and 48.00-h postdose. Similarly, the blood samples for evaluation of RAMI were drawn predose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 2.33, 2.50, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, and 12.00-h postdose. Ramiprilat was evaluated from the blood samples collected predose and at 0.33, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 2.33, 2.50, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 24.00, 48.00, and 72.00-h postdose.

As soon as possible following blood collection, samples were centrifuged at a temperature of 4°C and at ~ 1500 *g* for 10 min. The plasma obtained was separated into duplicate polypropylene culture tubes. The samples were frozen in an upright position and retained at a temperature of −20°C nominal until sent on dry ice to the bioanalytical facility for assay.

Bioanalysis

Sample preparation included a protein precipitation of BISO, RAMI and ramiprilat from human plasma, with their respective stable isotope-labeled (SIL) internal standards (IS), and analyzed by reversed-phase liquid chromatography coupled with mass spectrometry. The bioanalytical ranges for the analyses were established at 0.500–75.000 ng/ml for BISO, 0.100–50.000 ng/ml for RAMI, and 0.300–75.000 ng/ml for ramiprilat. The concentrations were calculated using a linear regression model with weighted least squares (1/x) for RAMI and ramiprilat and ($1/x^2$) for BISO. The bioanalytical assays were successfully validated according to regulatory guidance.

Sample size

For study 1 and study 2, a total of 64 enrolled subjects were anticipated to result in at least 60 completers, which would provide 90% power to show that the 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) were contained within the acceptance range of 80.00% to 125.00%. The calculations were based on the assumptions that the true GMRs would be within 0.95–1.05 and the intrasubject coefficient of variation (ISCV) would be about 32% for maximum concentration (C_{max}; calculated for RAMI). For the DDI (study 3), a total of 30 subjects were enrolled to have 24 completers and assess drug interaction.

PK statistical analysis

PK parameters were calculated from plasma concentrations by noncompartmental analysis based on actual times using Phoenix WinNonlin version 8.0 (Certara, Princeton, NJ). The PK parameters for BISO and RAMI were C_{max}, time to reach maximum concentration (T_{max}), area under the concentration time curve from time zero to the last quantifiable concentration, calculated using the linear trapezoidal method (AUC_{0-T}), apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration vs. time curve (λ_Z), area under the concentration time curve extrapolated to infinity, estimated as the sum of AUC_{0-T} and the extrapolated area calculated as a quotient of the last quantifiable concentration and λ_Z ($AUC_{0-\infty}$), and terminal elimination half-life, calculated as $\ln(2)/\lambda_Z$ (T_{half}). The PK parameters for ramiprilat were C_{max}, T_{max}, and area under the concentration time curve from time zero to the concentration at 72 h, calculated using the linear trapezoidal method (AUC_{0-72}). The natural logarithmic (ln) transformation of primary end points C_{max} and AUC_{0-T} for RAMI and BISO (study 1 and study 2) were used for inferential analysis using an analysis of variance (ANOVA) model, including subject effect (nested within sequence), treatment, period, as well as the sequence as fixed effect. The treatment, sequence, and period effects were evaluated at the

5% significance level. The ISCV was estimated based on the formula $\sqrt{e^{MSE}-1}$, where MSE is the mean square error obtained from the ANOVA model of the ln-transformed parameters. For ramiprilat, C_{max} and AUC_{0-72} were used as supportive information to the PK of the formulations (study 1 and study 2). C_{max}, AUC_{0-T}, and $AUC_{0-\infty}$ for BISO and RAMI and C_{max}, AUC_{0-72} for ramiprilat were used as PK end points for PK interaction assessment in study 3. Two-sided 90% CIs of the ratio of geometric least-squares means (LSmeans) calculated from the exponential of the difference between the comparisons of interest obtained from the ln-transformed primary PK parameters (C_{max} and AUC_{0-T}) were calculated for BISO and RAMI.

Study 1 and study 2 assessment of BE was based on the two one-sided tests with the null hypothesis of bioinequivalence at the 5% significance where the ratio of geometric LSmeans with corresponding 90% CI calculated for BISO and RAMI should all be within the acceptance range of 80.00% to 125.00%. For ramiprilat, the same criteria were applied, and the results were presented as supportive information to the PK of the formulations.

In study 3, the extent of PK interaction between the drugs was assessed descriptively based on the 90% CI calculated for BISO (BISO 10 mg + RAMI 10 mg vs. BISO 10 mg), RAMI and ramiprilat (BISO 10 mg + RAMI 10 mg vs. RAMI 10 mg). Statistical analyses were generated using SAS (version 9.4) using the general linear model procedure.

Safety

Safety was evaluated through assessment of adverse events (AEs), clinical laboratory test results (hematology, general biochemistry, and urinalysis), vital signs measurements, ECG findings, physical examination findings, and concomitant medication usage.

Co-prescription data analysis

The co-prescription analysis from the German market was conducted by IQVIA exclusively for Zentiva and the data have not been published yet. The co-prescription analysis was based on the number of recipes prescribed in Germany within the period of 3 years. The data are presented per each year as moving annual total (MAT) - a sum of 12 consecutive months from October 2017 until October 2019.

RESULTS

A total of 158 healthy male and female subjects were enrolled and received at least one treatment of which 11 subjects discontinued across the three studies (Table 1). Study 1 and study 2 randomized 64 subjects to two sequences of 32 subjects of which 64 received at least one treatment. Two and seven subjects did not complete study 1 and study 2, respectively. Study 3 randomized 30 subject to six sequences of five subjects and 28 subjects completed the study. The reason for discontinuation of the study was withdrawal of the subject (6%) and protocol deviation (0.6%, 1 subject did not receive the whole tablet of Concor 10 mg). Demographic baseline characteristics were well balanced among the three studies, with a majority of White men (Table 2).

Bioequivalence

Bisoprolol PK

The mean concentration-time profiles were almost identical following BISO/RAMI 10/10 or 10/5 mg FDC or when co-administered the single tablets over the studied 48-h interval (Figure 1a). BISO peak concentrations were achieved at 2.33 h after dosing decreasing steadily afterward with an estimated half-life ranging from 10.67 to 10.90 h across both treatments and studies (Table 3). GMR of AUC and C_{max} were contained within the BE predefined criteria (80.00%–125.00%; Table 3). The 90% CIs were close to unity for the primary end points for BE ranging from 98.29% to 103.57%, 97.89% to 103.44%, and 99.80% to 105.67% for C_{max}, AUC_{0-t}, and AUC_{inf}, respectively, following administration of a single oral dose of the FDC BISO/RAMI 10/10 mg and co-administration BISO 10 mg and RAMI 10 mg individual tablets (study 1). Similar results were obtained for the BISO/RAMI 10/5 mg FDC. investigation against the co-administration of BISO 10 mg and RAMI 5 mg individual tablets (study 2; Table 3).

Ramipril PK

The mean concentration-time profiles were almost the same following BISO/RAMI 10/10 or 10/5 mg FDC or when co-administered the single tablets over the studied 12-h interval (Figure 1b). Ramipril was rapidly absorbed with a peak concentration reached at a median of 0.50 h after dosing across both treatments and studies, decreasing quickly afterward with an estimated half-life ranging from 2.17 to 2.32 and 1.39 to 1.68 h following the 10 or 5 mg dose, respectively (Table 3). The GMRs of C_{max} and AUC were contained within the BE predefined criteria when BISO/RAMI 10/10 or 10/5 FDC were compared to the co-administration of BISO 10 mg and RAMI 10 mg or 5 mg individual tablets (80.00%–125.00%; Table 3). The 90% CIs were also within the

TABLE 1 Treatments and subject disposition of study 1, study 2, and study 3

Subject disposition	Study 1	Study 2	Study 3
Treatments			
Treatment A	BISO/RAMI 10/10 mg (test FDC)	BISO/RAMI 10/5 mg (test FDC)	BISO 10 mg (reference product)
Treatment B	BISO 10 mg + RAMI 10 mg (reference products administered concomitantly)	BISO 10 mg + RAMI 5 mg (reference products administered concomitantly)	RAMI 10 mg (reference product)
Treatment C	NA	NA	BISO 10 mg + RAMI 10 mg (reference products administered concomitantly)
Treatment allocation, *n* (%)	64 (100)	64 (100)	30 (100)
Subject completed the study, *n* (%)	62 (97)	57 (89)	28 (93)
Reason for study discontinuation			
Withdrawal by subject, *n* (%)	1 (2)	7 (11)	2 (7)
Protocol deviation	1 (2)	NA	NA
Population			
Safety population, *n* (%)	64 (100)	64 (100)	30 (100)
PK population, *n* (%)	62 (97)	58 (91)[a]	29 (97) for BISO 28 (93) for RAMI/Ramiprilat

Abbreviations: AUC, area under the concentration time curve; BISO, bisoprolol; C_{max}, maximum concentration; FDC, fixed-dose combination; NA, not applicable; PK, pharmacokinetic; RAMI, ramipril; T_{max}, time to maximum concentration.

[a]One subject withdrew consent after receiving both treatments, but without having completed the blood sampling schedule necessary for the complete characterization of the AUC and has therefore been retained in the PK analysis for C_{max}/T_{max} only.

TABLE 2 Demographic baseline characteristics of study 1, study 2, and study 3

Demographic	Study 1	Study 2	Study 3
Age (years), mean (SD)	38 (8)	35 (8)	43 (11)
Sex, *n* (%)			
Male	63 (98.4)	63 (98.4)	25 (83.3)
Female	1 (1.6)	1 (1.6)	5 (16.7)
BMI (kg/m^2), mean (SD)	26.2 (2.7)	25.7 (2.6)	26.1 (2.5)
Height (cm), mean (SD)	176.3 (6.7)	175.0 (7.4)	172.1 (10.1)
Weight (kg), mean (SD)	81.3 (9.5)	78.8 (9.3)	77.4 (11.3)
Race, *n* (%)			
White	54 (84.4)	48 (75.0)	27 (90.0)
Asian	2 (3.1)	3 (4.7)	2 (6.7)
Other	3 (4.7)	4 (6.3)	–
Black or African American	5 (7.8)	9 (14.1)	1 (3.3)

Abbreviation: BMI, Body mass index.

predefined acceptance range for C_{max}, AUC_{0-t}, and AUC_{inf}, following administration of a single oral dose of the FDC BISO/RAMI 10/5 mg and co-administration BISO 10 mg and RAMI 5 mg individual tablets. Similar results were obtained for the BISO/RAMI 10/10 mg FDC BE investigation against the co-administration of BISO 10 mg and RAMI 10 mg individual tablets with the exception of the lower bound of the 90% CI for C_{max} that was missed by 0.08% (79.92%; Table 3).

Ramiprilat PK

The active diacid metabolite of RAMI, ramiprilat, mean concentration-time profile was superimposed when the BISO/RAMI 10/10 or 10/5 mg FDC were compared to the single tablets co-administered (Figure 1c). Peak plasma ramiprilat concentrations were reached between 2.33 and 3-h after RAMI intake (Table 3). No elimination PK

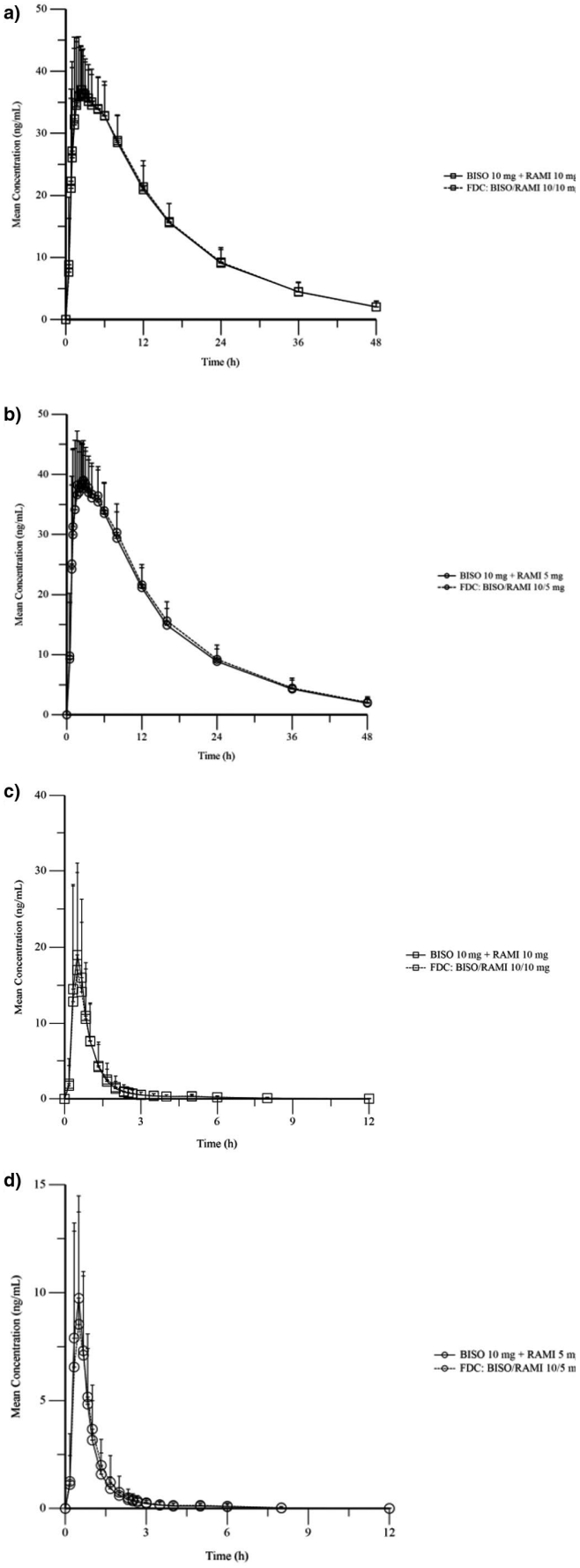

FIGURE 1 (a) Arithmetic mean ± SD of bisoprolol (BISO) concentration-time curve following single dose of the fixed-dose combination (FDC; BISO/ramipril [RAMI] 10/10 mg) compared to the free combination (study 1; open square BISO/RAMI 10/10 mg versus BISO 10 mg + RAMI 10 mg). (b) Arithmetic mean ± SD of bisoprolol concentration-time curve following single dose of the fixed-dose combination (BISO/RAMI 10/10 mg or 10/5 mg) compared to the free combination (study 2 open circle BISO/RAMI 10/5 mg vs. BISO 10 mg + RAMI 5 mg). (c) Arithmetic mean ± SD of RAMI concentration-time curve following single dose of the fixed-dose combination (BISO/RAMI 10/10 mg) compared to the free combination (study 1; open square BISO/RAMI 10/10 mg vs. BISO 10 mg + RAMI 10 mg). (d) Arithmetic mean ± SD of ramipril concentration-time curve following single dose of the fixed-dose combination (BISO/RAMI 10/10 or 10/5 mg) compared to the free combination (study 2; open circle BISO/RAMI 10/5 mg vs. BISO 10 mg + RAMI 5 mg)

parameters were estimated for ramiprilat as it was considered a long half-life substance, thus truncated AUC_{0-72} was estimated as a surrogate end point for exposure. Nonetheless, plasma was collected over a 72-h interval illustrating two of its three elimination phases; the initial rapid decline followed by its apparent elimination phase. Ramiprilat exposure (AUC) was in average 17- to 20-fold higher than RAMI in plasma. The GMR and 90% CIs for ramiprilat were within the standard acceptance BE range of 80.00%–125.00% (Table 3).

Drug-drug interaction

PK DDI results are shown in Table 4 along with the concentration-time curve of BISO and RAMI administered alone or together (Figure 2 and Supplementary Figure S3).

The single co-administration of BISO and RAMI 10 mg doses resulted in comparable C_{max} and AUCs for BISO and RAMI with no significant PK interaction when compared to the drug administered alone, as shown by GMRs ranging from 102.18% to 102.45% and 102.88% to 108.01%, respectively. The PK exposure of RAMI's active metabolite ramiprilat was not significantly influenced by the presence of BISO with GMRs ranging from 95.74% to 99.15% for C_{max} and AUC_{0-72}, respectively. All 90% CIs were also within the lack of predefined interaction boundaries (80%–125%).

Safety

Summary of AEs disposition experienced in each treatment arm of the three studies is presented in Table 5. A total of 34 treatment-emergent adverse events (TEAEs) were experienced by 14 of the 64 subjects (22%) who participated in study 1. Of these TEAEs, 17 occurred after

TABLE 3 PK parameters and GMRs (90% CIs) of BISO, RAMI, and ramiprilat following single dose of the FDC (BISO/RAMI 10/10 or 10/5 mg) compared to the free combination (study 1 and study 2)

PK parameters	Arithmetic mean (CV)		Least-squares mean ratio (90% CI)
BISO			
Study 1	**FDC BISO/RAMI (10 mg/10 mg)**	**BISO + RAMI (BISO 10 mg)**	**FDC/BISO + RAMI**
AUC_{0-t}, ng*h/ml	641.001 (16.2)	636.360 (16.6)	100.90 (98.29–103.57)
AUC_{inf}, ng*h/ml	674.730 (17.8)	671.134 (17.6)	100.63 (97.89–103.44)
C_{max}, ng/ml	42.844 (18.5)	41.774 (19.3)	102.70 (99.80–105.67)
T_{max},[a] h	2.33 (0.83–6.00)	2.33 (0.83–5.00)	–
$T_{1/2}$, h	10.67 (10.67)	10.90 (15.9)	–
Study 2	**FDC BISO/RAMI (10 mg/5 mg)**	**BISO + RAMI (BISO 10 mg)**	**FDC/BISO + RAMI**
AUC_{0-t}, ng*h/ml	662.128 (15.5)	643.441 (15.3)	102.86 (100.66–105.11)
AUC_{inf}, ng*h/ml	696.753 (16.9)	675.687 (16.2)	103.01 (100.72–105.35)
C_{max}, ng/ml	44.606 (15.3)	43.280 (20.7)	103.89 (100.52–107.36)
T_{max},[a] h	2.33 (0.83–6.00)	2.33 (0.83–6.00)	–
$T_{1/2}$, h	10.81 (15.9)	10.68 (15.0)	–
RAMI			
Study 1	**FDC BISO/RAMI (10 mg/10 mg)**	**BISO + RAMI (RAMI 10 mg)**	**FDC/BISO + RAMI**
AUC_{0-t}, ng*h/ml	16.059 (55.6)	16.775 (53.8)	94.24 (89.06–99.71)
AUC_{inf}, ng*h/ml	19.190 (54.2)	19.708 (53.2)	95.73 (88.68–103.33)
C_{max}, ng/ml	21.740 (65.8)	23.517 (56.9)	88.77 (79.92–98.60)
T_{max},[a] h	0.50 (0.33–1.67)	0.50 (0.33–1.33)	–
$T_{1/2}$, h	2.32 (51.2)	2.17 (38.9)	–
Study 2	**FDC BISO/RAMI (10 mg/5 mg)**	**BISO + RAMI (RAMI 5 mg)**	**FDC/BISO + RAMI**
AUC_{0-t}, ng*h/ml	7.836 (46.9)	7.640 (44.7)	101.75 (95.45–108.46)
AUC_{inf}, ng*h/ml	8.564 (50.0)	8.433 (52.3)	100.02 (89.98–111.19)
C_{max}, ng/ml	10.694 (54.5)	11.035 (41.4)	93.15 (85.09–101.97)
T_{max},[a] h	0.50 (0.33–1.67)	0.50 (0.33–0.83)	–
$T_{1/2}$, h	1.68 (77.5)	1.39 (69.4)	–
Ramiprilat			
Study 1	**FDC BISO/RAMI (10 mg/10 mg)**	**BISO + RAMI (RAMI 10 mg)**	**FDC/BISO + RAMI**
$AUC_{0-72\,t}$, ng*h/ml	231.631 (29.5)	231.373 (27.7)	99.54 (96.46–102.70)
C_{max}, ng/ml	25.384 (55.5)	25.250 (50.7)	96.95 (91.55–102.67)
T_{max},[a] h	2.42 (1.33–6.00)	2.33 (1.33–6.00)	–
Study 2	**FDC BISO/RAMI (10 mg/5 mg)**	**BISO + RAMI (RAMI 5 mg)**	**FDC/BISO + RAMI**
$AUC_{0-72\,t}$, ng*h/ml	126.648 (22.5)	125.093 (18.5)	100.06 (97.52–102.65)
C_{max}, ng/ml	8.158 (60.0)	7.893 (52.2)	99.70 (94.22–105.49)
T_{max},[a] h	3.00(1.67–8.00)	3.00(1.33–6.03)	–

Abbreviations: AUC_{0-t}, area under the plasma concentration–time curve from zero to time t; AUC_{inf}, AUC from zero to infinity; BISO, bisoprolol; CI, confidence interval; C_{max}, maximum plasma (peak) concentration; CV, coefficient of variation; FDC, fixed-dose combination; GMR, geometric mean ratio; PK, pharmacokinetic; RAMI, ramipril; $T_{1/2}$, terminal half-life; T_{max}, time to reach C_{max} or maximum response following drug administration.

[a]Median (minimum, maximum).

TABLE 4 Parameters and GMRs (90% CIs) of BISO, RAMI, and ramiprilat following single dose of BISO (10 mg) and RAMI (10 mg) alone or in combination (study 3)

PK parameters	Arithmetic mean (CV)		Least-squares mean ratio (90% CI)
BISO			
Study 3	**BISO 10 mg + RAMI 10 mg**	**BISO 10 mg alone**	**BISO 10 mg + RAMI 10 mg/ BISO 10 mg alone**
AUC_{0-t}, ng*h/ml, $n = 29$	751.044 (20.2)	732.301 (18.5)	102.18 (100.22–104.18)
AUC_{inf}, ng*h/ml, $n = 29$	798.707 (20.7)	776.722 (18.5)	102.35 (100.17–104.56)
C_{max}, ng/ml, $n = 29$	43.526 (19.4)	42.638 (21.4)	102.45 (99.29–105.71)
T_{max},[a] h, $n = 29$	2.50 (1.00–5.00)	2.33 (1.00–5.00)	–
$T_{1/2}$, h, $n = 29$	11.32 (12.6)	11.20 (13.3)	–
RAMI			
Study 3	**BISO 10 mg + RAMI 10 mg**	**RAMI 10 mg alone**	**BISO 10 mg + RAMI 10 mg/ RAMI 10 mg alone**
AUC_{0-t}, ng*h/ml, $n = 28$	18.032 (34.6)	17.121 (34.0)	108.01 (93.38–124.93)
AUC_{inf}, ng*h/ml, $n = 12$	18.741 (29.8)	18.129 (31.3)	105.54 (96.68–115.21)
C_{max}, ng/ml, $n = 28$	25.606 (47.8)	24.053 (40.6)	102.88 (88.49–119.62)
T_{max},[a] h, $n = 28$	0.50 (0.33–3.00)	0.50 (0.33–0.83)	–
$T_{1/2}$, h, $n = 12$	1.91 (53.0)	2.03 (42.4)	–
RAMI			
Study 3	**BISO 10 mg +RAMI 10 mg**	**RAMI 10 mg alone**	**BISO 10 mg +RAMI 10 mg / RAMI 10 mg alone**
$AUC_{0-72\,t}$, ng*h/ml, $n = 28$	208.160 (21.9)	211.528 (27.4)	99.15 (94.13–104.43)
C_{max}, ng/ml, $n = 28$	21.602 (48.3)	24.108 (67.2)	95.74 (84.61–108.34)
T_{max},[a] h, $n = 28$	2.50 (1.33–5.00)	2.50 (1.33–6.00)	–

Abbreviations: AUC_{0-t}, area under the plasma concentration–time curve from zero to time t; AUC_{inf}, AUC from zero to infinity; BISO, bisoprolol; CI, confidence interval; C_{max}, maximum plasma (peak) concentration; CV, coefficient of variation; GMR, geometric mean ratio; PK, pharmacokinetic; RAMI, ramipril; $T_{1/2}$, terminal half-life; T_{max}, time to reach C_{max} or maximum response following drug administration.

[a]Median (min, max).

administration of FDC BISO/RAMI 10/10 mg and the free combination. Most of the TEAEs experienced during the study were considered drug-related (32/34; 94%). The TEAEs experienced during the study were deemed mild (30/34, 88%) and moderate (4/34, 12%) in intensity. A total of 30 TEAEs were experienced by 16 of the 64 subjects (25%) who participated in study 2. Of these TEAEs, 10 occurred after administration of FDC BISO/RAMI 10/5 mg and 20 occurred after administration of the free combination. Most of the TEAEs experienced during the study were considered drug-related (21/30; 70%). The TEAEs experienced during the study were deemed mild (27/30; 90%) and moderate (3/30; 10%) in intensity. Last, a total of 22 TEAEs were experienced by eight (27%) of the 30 subjects who participated in study 3. Of these TEAEs, eight occurred after administration of BISO 10 mg alone, six occurred following administration of RAMI 10 mg alone, and eight occurred after administration of the BISO 10 mg + RAMI 10 mg. Most of the TEAEs experienced during the study were considered drug-related (16/22; 73%). The TEAEs experienced during the study were all deemed mild in intensity. Overall, none of the subjects experienced a severe TEAE during the three studies. All TEAEs experienced during the three studies were resolved or were recovered at the end of the study with the exception of one event, which had an unknown outcome due to the subject being lost to follow-up during study 2.

Co-prescription

Co-prescription data showed that ~ 20% of patients taking BISO are also taking RAMI in combination, whereas about 14% of patients taking RAMI are also using BISO in combination (Figure 3). The share of BISO/RAMI particular strengths 5/5, 5/10, 10/5, and 10/10 mg on the total amount of co-prescriptions of BISO and RAMI was ~ 66%, 17%, 8%, and 9%, respectively (Supplementary Figure S4).

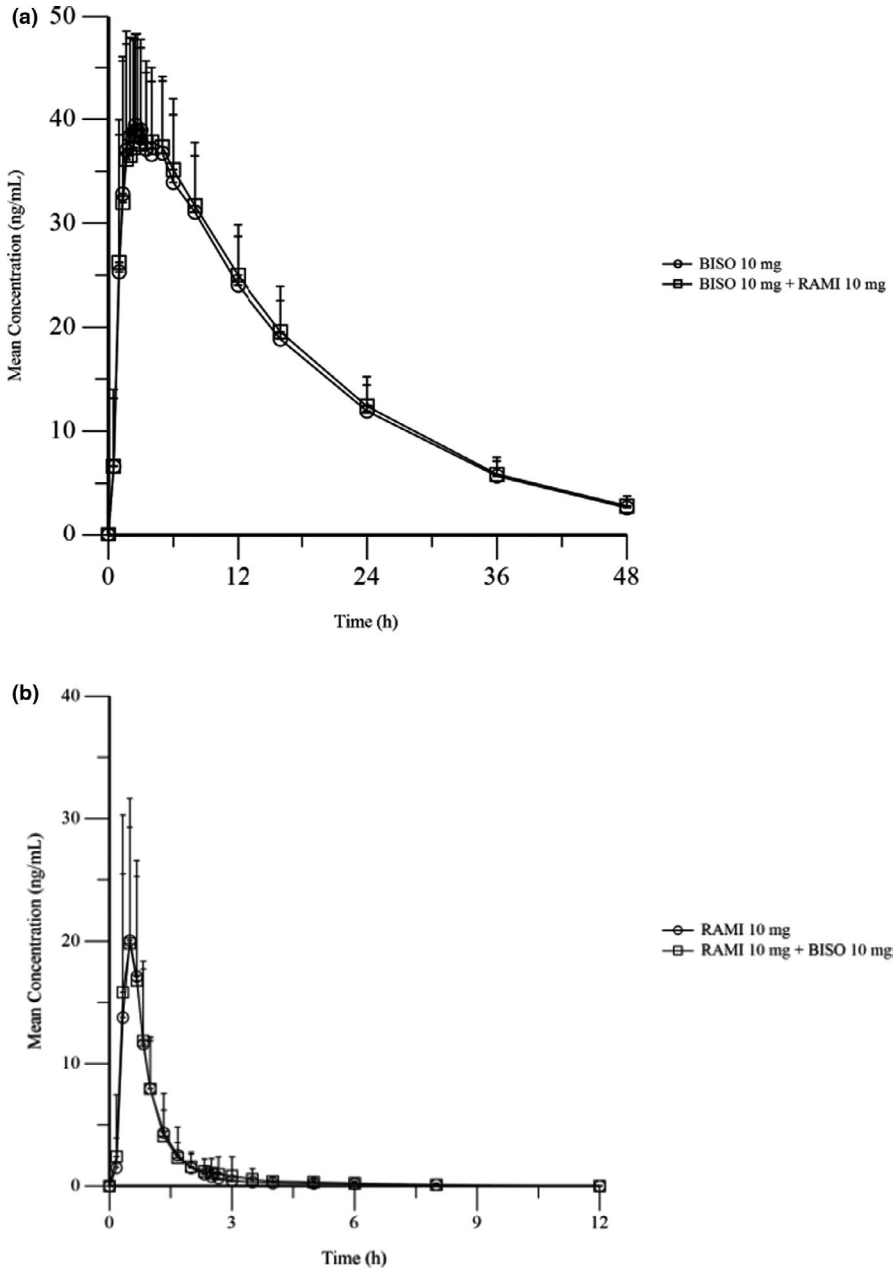

FIGURE 2 (a) Arithmetic mean ± SD of bisoprolol (BISO) concentration-time curve following single dose of BISO (10 mg) and ramipril (RAMI; 10 mg) alone or in combination (study 3). (b) Arithmetic mean ± SD of ramipril concentration-time curve following single dose of BISO (10 mg) and RAMI (10 mg) alone or in combination (study 3)

DISCUSSION

Guidelines on management of arterial hypertension promote the use of combination therapy, including the use of a BB and ACEI supported by the evidence of additive effects when co-administered from their complementary mechanism of action targeting different BP control systems.[5,6] Bisoprolol is indicated in the treatment of stable chronic mild to moderate heart failure with reduced systolic left ventricular function, hypertension, and angina.[28,30] Bisoprolol selectively blocks beta-1 adrenoceptor on the cardiac myocyte thus regulating cardiac rate and contractility.[31] Ramipril is indicated in the treatment of several diseases, such as hypertension and congestive heart failure by inhibition of the angiotensin-converting enzyme leading to vasodilation.[29] Co-prescription data showed a wide clinical experience with concomitant use of BISO and RAMI in the strengths 5/5, 5/10, 10/5, and 10/10 mg (data not published). The combined use of BISO and RAMI in an FDC is expected to increase adherence, thus clinical outcome by decreasing the burden of multiple pill's management.[32] Thus, a novel FDC of BISO and RAMI in four different strengths (BISO/RAMI 10/10, 10/5, 5/10, and 5/5 mg) was developed for the treatment of arterial hypertension. The product is primarily intended for the patients adequately controlled with BISO and RAMI individual products, however, it is also suitable for initial combination treatment in patients who may benefit from the combination of BBs and ACEI. Two BE trials, evaluating PK between the new FDC BISO/RAMI and co-administered BISO and RAMI as separate tablets, along

TABLE 5 Summary of TEAEs disposition and intensity observed during study 1, study 2, and study 3

Measure	Study 1		Study 2		Study 3		
	FDC BISO/RAMI (10/10 mg)	BISO + RAMI (10 mg + 10 mg)	FDC BISO/RAMI (10/5 mg)	BISO + RAMI (10 mg + 5 mg)	Bisoprolol 10 mg alone	Ramipril 10 mg alone	BISO + RAMI (10 mg + 10 mg)
TEAEs reported, *n*	17	17	10	20	8	6	8
Subjects with at least one drug-related TEAE, *n* (%)][a]	8 (12.9)	10 (15.6)	4 (6.6)	9 (14.8)	4 (13.8)	3 (10.7)	5 (16.7)
TEAEs Relationship[b]							
Related, *n* (%)[a]	16 (94.1)	16 (94.1)	7 (70.0)	14 (70.0)	5 (62.5)	5 (83.3)	6 (75.0)
Not related, *n* (%)	1 (5.9)	1 (5.9)	3 (30.0)	6 (30.0)	3 (37.5)	1 (16.7)	2 (25.0)
TEAEs by severity/intensity[b]							
Mild, *n* (%)	16 (94.1)	14 (82.4)	9 (90.0)	18 (90.0)	8 (100.0)	6 (100.0)	8 (100.0)
Moderate, *n* (%)	1 (5.9)	3 (17.6)	1 (10.0)	2 (10.0)	0	0	0
Severe, *n* (%)	0	0	0	0	0	0	0

Abbreviations: BISO, bisoprolol; FDC, fixed-dose combination; RAMI, ramipril; TEAE, treatment emergent adverse events.

[a]Percentages are based on the number of subjects in the Safety population in each treatment group. Drug-related TEAE that was reported as: reasonable possibility.[b]Percentages are based on the total number of TEAEs reported in each treatment group.

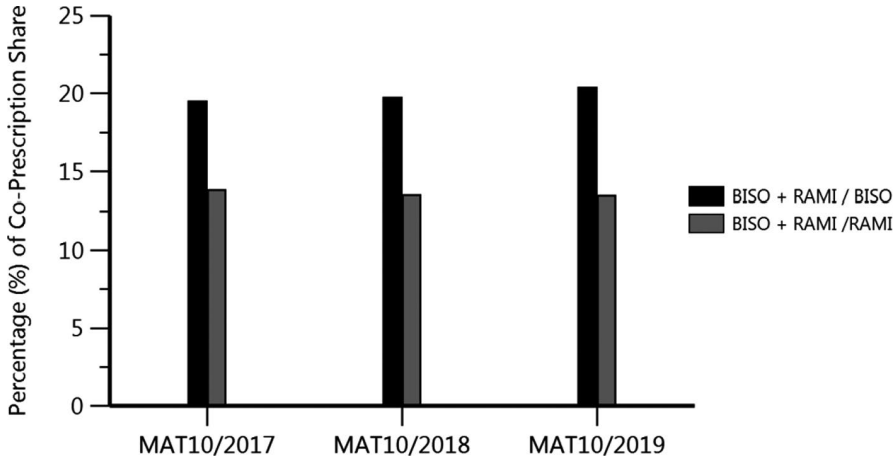

FIGURE 3 Share of co-prescription of bisoprolol/ramipril (BISO/RAMI) versus co-prescription of both individual products across all strengths

with a DDI trial were performed to bridge concurrent use of both products to a single FDC product and confirm lack of clinically significant interaction between BISO and RAMI.

The bioavailability of two strengths of BISO/RAMI FDC (10/10 and 10/5 mg) was investigated in two BE studies against individual reference products in respective strengths, remaining strengths of BISO/RAMI FDC (5/10 and 5/5 mg) were the subject of biowaiver request. The highest available strengths of both reference products were used in the DDI study, as they represent the most extreme combination and would best reveal a potential interaction between drugs. In order to best detect potential differences between formulations and with regard to the intended method of administration independently on food intake, both BE studies were conducted under fasting conditions. The same conditions were applied also for the DDI study in order to detect most sensitively a potential interaction between both compounds. The evaluation of BE was based upon measured concentrations of the parent compounds BISO and RAMI. Ramiprilat, the active metabolite of RAMI, was also measured to provide supportive information to the PK.

Clinical PK findings showed that FDC was BE for BISO in both strengths, either combined with RAMI 10 or 5 mg, to the free-combination as the rate and extent of absorption were not significantly different (90% CI contained within the predefined BE acceptance range of 80.00%–125.00%) for C_{max} and AUC following a single oral dose under fasting conditions. Ramipril C_{max} and AUC was also found to be within the predefined limits of BE for the BISO/RAMI 10/5 mg when compared to the free-combination, whereas for the BISO/RAMI 10/10 mg, although the GMRs were all within the BE limits for C_{max} and AUC, the 90% CI for C_{max} were not entirely within the BE limits (lower bound was 79.92%). The observed ISCV (36%) was higher than expected (32%) for this study.

For ramiprilat, the active metabolite of RAMI, peak and extent of absorption were within the BE limits in both BE studies. Based on the root cause analysis, a lower rate of absorption of RAMI may be caused by the excipients forming an insoluble microstructure during the dissolution phase and thus slightly decelerating the dissolution rate of RAMI. As RAMI is characterized by a very prompt T_{max}, this phenomenon may play an important role for the rate of absorption. The rate of absorption of RAMI was decreased for both strengths tested in BE studies. Whereas the lower strength 10/5 mg was still concluded as BE to the reference products, the higher strength 10/10 mg containing double amount of RAMI did not slightly fulfill BE criteria.

No clinically significant PK interaction was observed between BISO and RAMI following a single dose administration in healthy subjects. The single dose regimen was selected to examine the potential interaction on the level of absorption. Both compounds have different metabolic and elimination pathways (BISO is mainly metabolized by CYP450[33]; RAMI is rapidly hydrolyzed by carboxylesterases and uridine 5'-diphospho-glucuronosyltransferase, and to a minor extent by CYP450[27,33]), and they are both not known as inhibitors or inducers of CYP450. The potential for interaction was hypothesized to be absent and was confirmed during this DDI study. The DDI study is, to our knowledge, the first dedicated trial to demonstrate lack of PK interaction between BISO and RAMI. Although a majority of enrolled subjects were male, gender differences documented for cardiovascular drugs[34] are not expected to have influence on the outcome, as the study was designed in a cross-over fashion. The FDC was well-tolerated in both BE studies. No unexpected safety findings were noted, and there was no indication of safety differences between the FDC tablets and the corresponding combinations of single-component tablets of BISO and RAMI.

CONCLUSION

Based on the results, BISO/RAMI FDC 10/5 mg is judged to be BE to the individual reference products Concor

10 mg and Delix 5 mg taken concomitantly under fasting conditions. As the lower CI for C_{max} of RAMI was very slightly outside the predefined BE limit, BISO/RAMI FDC 10/10 mg is judged not to be BE to the individual reference products Concor 10 mg and Delix Protect 10 mg taken concomitant under fasting conditions.

The single co-administration of BISO and RAMI 10 mg doses resulted in comparable rate and extent of absorption for BISO and RAMI when compared to individual products with no significant PK interaction. The PK exposure of RAMI's active metabolite ramiprilat was not significantly influenced by the presence of BISO. Therefore, it may be concluded that no PK interaction was observed between BISO and RAMI/ramiprilat.

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CONFLICT OF INTEREST

J.S., J.B., and T.H. are employees of Zentiva, k.s. sponsored the clinical trial. J.H., B.S., and E.S. are employees of Altsciences. Zentiva, k.s. sponsored the clinical trial at Altasciences Contract Research Organization.

AUTHOR CONTRIBUTIONS

J.S. and J.H. wrote the manuscript. J.S., J.H., J.B., T.H., B.S., and E.S. designed the research. J.S., J.B., T.H., and E.S. performed the research. J.S., J.H., and B.S. analyzed the data.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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