CLINICAL STUDY REPORT

SYNOPSIS

Study CRO-PK-23-364 – Sponsor code NEB-RAM-01

Bioequivalence of Nebivolol and Ramipril following their oral co-administration as fixed and extemporaneous combination in healthy subjects

Open-label, randomized, two-treatment, three-period, three-sequence, single dose, partial replicate cross-over study

Test investigational medicinal product:	Nebivolol/Ramipril 5/10 mg Fixed Dose Combination (FDC)
Reference investigational medicinal product:	Nebivolol 5 mg + Ramipril 10 mg as extemporaneous combination (EC)
Sponsor:	MENARINI RICERCHE S.p.A., Via Sette Santi, 1 50131 Firenze, Italy
Principal Investigator:	Dr. Milko Radicioni MD, PhD CROSS Research S.A., Phase I Unit, Via F. A. Giorgioli 14, CH-6864, Arzo (TI), Switzerland Phone: +41.91.64.04.450 Email: clinic@croalliance.com
Development phase:	Phase I, Bioequivalence Study
First subject first visit	26JUN23
Last subject last visit	16OCT23
Version and date:	Final version 1.0, 16MAY2024

This study was conducted in compliance with the protocol, the principles of Good Clinical Practice (GCP) [ICH topic E6 (R2)], and with the local regulatory requirements

This document contains 293 pages plus appendices

2 SYNOPSIS

Name of Company: MENARINI RICERCHE S.p.A., Italy	**TABULAR FORMAT**		**(For National Authority Use only)**
Name of Finished Product: Nebivolol/Ramipril 5/10 mg FDC	**REFERRING TO PART OF THE DOSSIER**	5.3	
Name of active substance(s): Nebivolol; Ramipril	**Volume:**		
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Title of the study:
Bioequivalence of Nebivolol and Ramipril following their oral co-administration as fixed and extemporaneous combination in healthy subjects

Investigator(s) and centre(s):
Milko Radicioni, MD; CROSS Research Phase I Unit, Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland

Publication (reference):

Studied period (years):	**Date of first enrolment: 26JUN23** **Date last vol. completed: 16OCT23**	**Phase of development:**
2023		**I**

Objectives:
Primary objective:
Evaluation of the bioequivalence of the Nebivolol (NEB)/Ramipril (RAM) 5/10 mg Fixed Dose Combination (FDC) (Test) versus NEB 5 mg + RAM 10 mg Extemporaneous Combination (EC) (Reference).
Secondary objective:
Evaluation of the safety and tolerability of single oral doses of NEB 5 mg co-administered with RAM 10 mg as FDC and EC in healthy subjects.

Methodology:
Open label, randomized, two-treatment, three-period, three-sequence, single-dose, partial replicate cross-over study

Number of subjects (planned and analysed):
Fifty-four (54) subjects, i.e. 18 for each treatment sequence, were randomised in the study as planned. The 18 subjects randomised in each of the 3 sequences received at least one dose of investigational product and were included in the safety population. All 18 subjects in sequence B, and 16 out of the 18 randomised subjects in sequence A and sequence C completed the study per protocol and were included in the PK population for all three analytes. Two subjects, one in sequence A and another in sequence C, discontinued the study due to TEAEs. The other 2 subjects, one in sequence A and another in sequence C, withdrew consent to study participation. As per pre-defined exclusion criteria, two additional subjects were excluded from the PK population for Ramiprilat (sequence B) due to the presence of pre-dose concentrations higher than 5% the Cmax.

Diagnosis and criteria for inclusion:
Inclusion criteria:
1. Properly executed written informed consent form (ICF).
2. Healthy males and females aged 18 to 60 years, inclusive, at Screening.
3. BMI between 18.5 kg/m^2 and 30 kg/m^2, inclusive, and weight of at least 50 kg at Screening.
4. Normal metabolizers for CYP2D6 based on the genotype.
5. Negative pregnancy test for women of childbearing potential.
6. Females of child-bearing potential had to use at least one of the following reliable methods of contraception:
   - Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
   - A non-hormonal intrauterine device [IUD] or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
   - A male sexual partner who agreed to use a male condom with spermicide
   - A sterile sexual partner

SYNOPSIS (cont.)

Name of Company: MENARINI RICERCHE S.p.A., Italy	**TABULAR FORMAT**		**(For National Authority Use only)**
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Diagnosis and criteria for inclusion, continued:
Inclusion criteria, continued:

- True abstinent. True (long term) heterosexual abstinence, defined as refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject, while periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), lactational amenorrhea and withdrawal are not acceptable

7. Women of non-child-bearing potential or in post-menopausal status defined as such when there is either:
   - 12 months of spontaneous amenorrhea or
   - 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or
   - 6 weeks documented postsurgical bilateral oophorectomy with or without hysterectomy were admitted
8. Male participants with a partner of childbearing potential had to agree to use a barrier method (condom with spermicidal cream) when sexually active while participating in the study, unless they were sterile.
9. Non-smokers/non-users of nicotine containing products and non-users of Vapo e-cigarettes (defined as a non-smoker/non-user during the last three months before Screening).
10. Considered by the Investigator to be in good health for participation in this study, i.e. absence of clinically significant diseases or clinically significant abnormal laboratory values, as per medical history review, physical examination, vital signs, electrocardiograms (ECG) tracing, and clinical laboratory findings.
11. Systolic blood pressure (SBP) ≥ 90 mmHg and diastolic blood pressure (DBP) ≥ 60 mmHg; Pulse Rate (PR) ≥ 50 bpm.
12. Willing and able to comply with all study requirements, schedules and procedures.

Exclusion criteria:

1. Subjects with history of allergy, photoallergy or phototoxicity, idiosyncrasy or hypersensitivity to the study drugs, or any of the excipients of the study drug products (lactose monohydrate included).
2. History or clinical evidence of cardiovascular, respiratory, renal, hepatic, endocrine, metabolic, gastrointestinal, haematological, bleeding disorders, neurological or psychiatric pathology or other chronic diseases that, in the opinion of the Investigator, could jeopardize or would compromise the participant's ability to participate in this study.
3. History of angioedema (hereditary, idiopathic or secondary to treatment with ACE inhibitors or angiotensin II receptor antagonists).
4. History of orthostatic hypotension (orthostatic hypotension is defined as a drop of at least 20 mm Hg in SBP or a drop of at least 10 mm Hg in DBP within two to five minutes of standing, or if standing causes at least moderate symptoms, i.e. light-headedness, visual blurring, dizziness, generalized weakness, fatigue, cognitive slowing, leg buckling, coat-hanger ache, and gradual or sudden loss of consciousness)
5. Any condition which might interfere with the absorption, distribution, metabolism or excretion of the drugs, according to the Investigator's opinion.
6. Surgery within the previous 6 months, blood loss > 450 mL within the previous 3 months before treatment start (i.e., first dosing) or active bleedings (except menstruations).
7. Having donated blood or received transfusion of any blood products within 3 months and/or having donated plasma within 7 days before Screening.
8. Positive serology to Human Immunodeficiency Virus (HIV) I and II, Hepatitis B Virus (HBV) (i.e. positive for HBsAg or HBcAb) or Hepatitis C Virus (HCV).
9. History of drug, alcohol [>1 drink/day for females and >2 drinks/day for males, defined according to the USDA Dietary Guidelines 2020-2025], caffeine abuse (>5 cups coffee/tea/day)

SYNOPSIS (cont.)

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Diagnosis and criteria for inclusion, continued:
Exclusion criteria, continued:

10. Use of caffeine- or xanthine-containing products (e.g. tea, coffee, cola, chocolate) and not suitable to abstain from such products consumption 48 h before dosing with study treatments and for 72 hours of each PK study session.
11. Abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians
12. Positive result of drugs of abuse on urine screening test for cocaine and metabolites (COC 300), Amphetamine (AMP 500), Methamphetamine (MET 500), Marijuana (including Cannabinoids THC) (THC 50), Opiates (including Heroin Morphine and metabolites) (MOP 300), Methylenedioxymethamphetamine Ecstasy (MDMA 500), Methadone (MTD 300), or positive result in alcohol salivary test or cotinine urine test.
13. Females of childbearing potential who were not using any of the highly effective contraceptive methods (see inclusion criterion 6).
14. Breast-feeding and pregnant females as per positive β-HCG (Beta-subunit Of Human Chorionic Gonadotropin) results at Screening or Admission (first residence in the Unit before first dosing).
15. Taking any pharmacological treatment, within 21 days or 5 half- lives of the product, whichever was longer, prior to dosing (except for symptomatic short-term paracetamol use, up to 1.5 g/day, and hormonal contraception as per inclusion criterion 6).
16. Intake of any herbal product/preparation, food supplement in the last 14 days prior to the dosing.
17. Subjects receiving concomitant treatment with other investigational medicinal product (IMP) or who received the last dose of the IMP in the last 3 months calculated as the time between the first calendar day of the month that followed the last visit of the previous study and the first day of the present study (or 5 half-lives of the IMP, whichever is longer) before Screening.
18. Poor, intermediate and ultra-rapid metabolizers for CYP2D6 based on the genotype.
19. Any subject who, in the judgement of the Investigator, was likely to be non-compliant with study procedures and/or restrictions, or unable to cooperate because of e.g. language problem or poor mental development.
20. Any subject who could not be contacted in case of emergency.
21. Vulnerable subject defined as a subject kept in detention, a protected adult under guardianship/trusteeship or committed to an institution by governmental or juridical order.
22. Employee or family member of the Sponsor or the involved contract research organization (CRO).
23. Subject having positive test for Covid-19 confirmed by locally-accepted standard testing procedures within the last 48 hours prior to Screening and prior to each Admission to the Clinical Unit, or who had clinical signs and symptoms consistent with Corona-Virus Disease 2019 (COVID-19), e.g. fever, dry cough, dyspnoea, sore throat, fatigue or a Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection confirmed by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) or rapid antigen test in the last 2 weeks prior to Screening.

Test product, batch number:
Nebivolol (NEB)/Ramipril (RAM) 5/10 mg film-coated tablet Fixed Dose Combination (FDC), Menarini, Menarini Ricerche S.p.A., Italy. Batch N. T1023041, Expiry date May 2024

Reference product, batch number:
Nebilet® (NEB 5 mg film-coated tablet), Berlin-Chemie Menarini Hrvatska d.o.o., Croatia, plus Cardace® (RAM 10 mg tablet), Sanofi-Aventis Latvia SIA, Latvia – Extemporaneous combination (EC).
Batch N. T1023042, Expiry date November 2024.

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Name of Company: MENARINI RICERCHE S.p.A., Italy	**TABULAR FORMAT**		**(For National Authority Use only)**
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Dose, mode of administration:
During each of 3 PK sessions, each subject took one NEB/RAM 5/10 mg FDC film-coated tablet (Test) or the corresponding extemporaneous combination of the two mono components, i.e. NEB 5 mg+ RAM 10 mg EC (Reference), according to the three-period, three-sequence, partial replicate study design. A minimum of 14-day wash-out period between each IMP intake was requested. Sequence of treatments followed the randomization list and is presented in the following table:

	Study Sessions		
	1	**2**	**3**
Sequence A	NEB/RAM 5/10 mg FDC	NEB 5 mg + RAM 10 mg EC	NEB 5 mg + RAM 10 mg EC
Sequence B	NEB 5 mg + RAM 10 mg EC	NEB 5 mg + RAM 10 mg EC	NEB/RAM 5/10 mg FDC
Sequence C	NEB 5 mg + RAM 10 mg EC	NEB/RAM 5/10 mg FDC	NEB 5 mg + RAM 10 mg EC

NEB: Nebivolol; RAM: Ramipril

The Test and the Reference products were taken as single doses in the morning, at 8:00 a.m., in fasting condition, and swallowed by the subjects in a sitting or upright position with a total volume of 240 mL of still water.
The two tablets of the EC were taken almost simultaneously, i.e. one immediately after the other, with Nebivolol tablet taken first, followed by Ramipril tablet. The intake time was recorded for each drug.

Study endpoints
Primary pharmacokinetic endpoints

- Area Under the plasma concentration-time Curve from time zero (baseline) to the last quantifiable time point ($AUC_{(0-t)}$) and maximum plasma concentration (C_{max}) of NEB and RAM when administered as FDC film-coated tablet (Test) and as EC tablets (Reference).

Secondary pharmacokinetic endpoints

- Relevant secondary standard pharmacokinetic parameters of NEB and RAM such as AUC from time zero to infinity ($AUC_{(0-\infty)}$), AUC from time zero to 72h ($AUC_{(0-72)}$), for NEB only, plasma terminal half-life ($t_{1/2}$), terminal elimination rate constant (λ_z), residual area ($\%AUC_{extrap}$) and time to maximum plasma concentration (t_{max}) when NEB and RAM are administered as Test and Reference formulations.

Exploratory pharmacokinetic endpoints

- AUC from time zero to 72h ($AUC_{(0-72)}$), t_{max}, λ_z, $t_{1/2}$ and C_{max} of Ramiprilat when NEB and RAM are administered as Test and Reference formulations.
- Other PK parameters for all the analytes could be derived if considered appropriate at the time of the analysis.

Safety endpoints:
Incidence, intensity (severity), seriousness and treatment causality of Treatment Emergent Adverse Events (TEAEs), i.e. AEs that occur after the first study drug intake.
Changes in laboratory safety parameters, vital signs and 12-lead ECG versus baseline.

Analytics: Blood samples for plasma Nebivolol and Ramiprilat determinations were collected at pre-dose (0), 5, 15, 30, 45 min and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 48 and 72 h post-dose. Blood collection for plasma Ramipril analysis was performed at the same time-point up to 24 h post-dose. Analyses were performed at Anapharm Europe, S.L.U., Spain, using fully validated LC-MS/MS methods, and in compliance with GCP regulations, following applicable GLP principles.

SYNOPSIS (cont.)

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Statistical methods:
The data documented in this study and the parameters measured were presented using classic descriptive statistics for quantitative variables, and frequencies (i.e., count and percentages) for qualitative variables. Pharmacokinetic (PK) parameters were calculated using Phoenix WinNonlin® version 8.3.5. The analysis of demographic, PK parameters and safety data was performed using SAS® version 9.04.01.

Analysis sets:
Safety population: All subjects who received at least one administration of study treatment.
Pharmacokinetic (PK) population: All subjects who have evaluable and reliable concentration-time data for deriving the study primary PK parameters for both the Reference and Test formulations and who did not experience major protocol violations or events impacting the PK results.

Pharmacokinetic analysis:
All PK parameters and variables were summarized by descriptive statistics including: arithmetic mean, Standard Deviation (SD), Coefficient of Variation (CV%), geometric mean (GM), geometric SD, geometric CV% and its 90% Confidence Interval (CI), minimum, median and maximum, as appropriate.
Concentrations and PK parameters were determined following partial replicated administration of Test and Reference formulations, as appropriate, by period. This means that there are 2 PK profiles for EC and one PK profile for FDC. Pharmacokinetic parameters for Nebivolol, Ramipril and Ramiprilat were derived from individual measured concentrations by non-compartmental analysis (NCA) using Phoenix™ WinNonlin® software, version 8.3.5.

Analysis of the Primary PK variables:
To evaluate the bioequivalence of NEB/RAM 5/10 mg FDC vs. NEB 5 mg + RAM 10 mg EC, natural log transformed C_{max} and $AUC_{(0-t)}$ of NEB and RAM were analysed using a mixed effect model including sequence, period and formulation as fixed effects and subject (sequence) as a random effect, also taking into account the partial replicate design. Estimates of the mean difference (Test formulation – Reference formulation) and corresponding 90% CIs were obtained from the model for each analyte. The mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of geometric means (GMR; Test formulation/Reference formulation) and 90% corresponding CIs. Bioequivalence could be concluded for NEB/RAM 5/10 mg FDC vs. NEB 5 mg + RAM 10 mg EC, if the 90% CI for the ratio of geometric means for both C_{max} and $AUC_{(0-t)}$ of NEB and RAM fell entirely within the bioequivalence acceptance range (80.00-125.00%). Intra-subject variability of RAM C_{max} has been reported as higher than 30%, suggesting that RAM might be a highly variable drug product (HVD). Thus, according with the EMA guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), the bioequivalence acceptance limits for RAM C_{max} could be widened since the observed intra-subject CV% for the Reference was confirmed as > 30%, according to the formula: [U, L] = exp [±k·sWR], where U and L are the upper and lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the observed within-subject standard deviation of the log-transformed values of C_{max} of the Reference product, obtained as $\sqrt{ln(CV^2+1)}$. Widened C_{max} 90% CIs were therefore calculated on the basis of the calculated intra-subject Reference CV%.
On the other hand, the GMR for RAM C_{max} and the GMR and 90% CI for $AUC_{(0-t)}$ should lie within the conventional bioequivalence acceptance range 80.00-125.00%.

Analysis of Secondary PK variables: The following secondary PK variables for the analytes Nebivolol and Ramipril were compared when administered as FDC tablet vs. EC:

- $AUC_{(0-\infty)}$ was analysed similarly to $AUC_{(0-t)}$.
- The other PK parameters were summarized descriptively.

Analysis of Exploratory PK variables: Exploratory PK parameters were summarized descriptively. The bioequivalence test was performed also for Ramiprilat, for exploratory purposes.

Analysis of Safety variables: Safety variables and changes from baseline, when applicable, were summarized by descriptive statistics.

SYNOPSIS (cont.)

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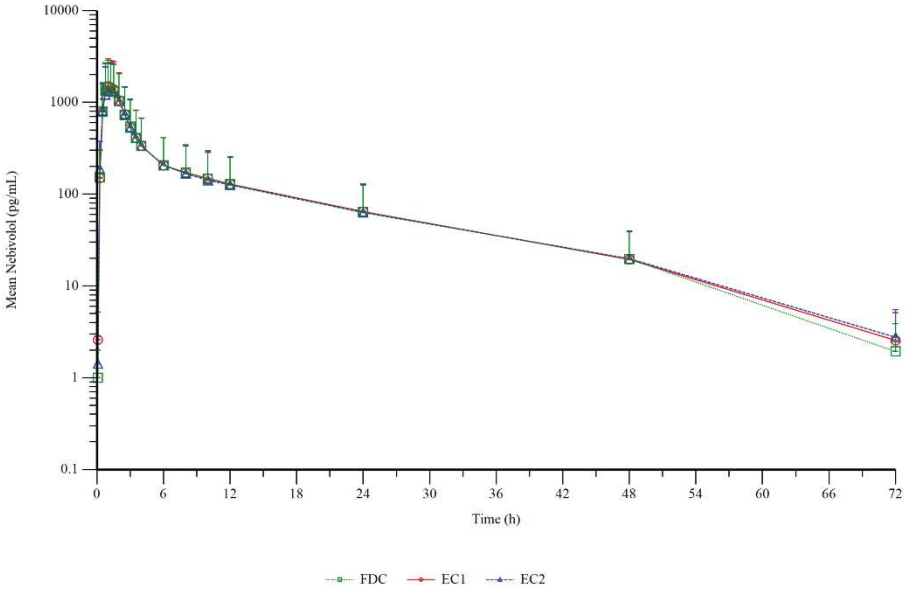
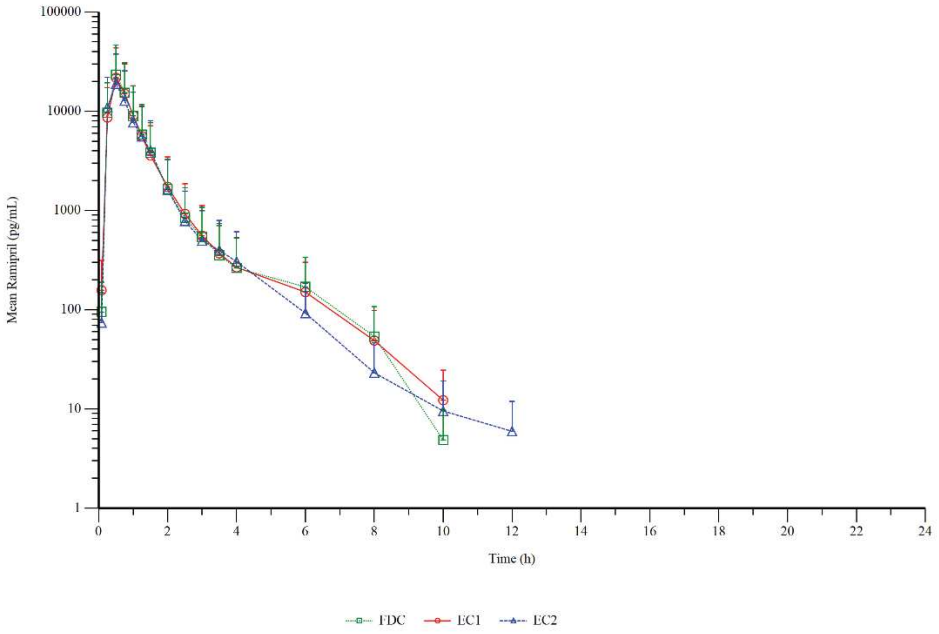
Results: ***Pharmacokinetic primary and secondary endpoints results***

Mean (+SD) Nebivolol and Ramipril plasma concentration-time profiles up to 72 h and 24 h, respectively, after single oral dose of the Test and Reference products are shown in the figures below (semilogarithmic scale).





SYNOPSIS (cont.)

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Results:

Pharmacokinetic primary and secondary endpoints results, continued

Main **Nebivolol** plasma PK parameters and results of the bioequivalence test between FDC and EC are summarised in the following table:

PK parameter	**FDC**	**EC1**	**EC2**	**Overall intra-subject CV%, intra-subject CV% within Reference**	**GMR***	**90%CI**
C_{max} (pg/mL)	1571.5 ±1.31	1680.52 ±1.36	1569.7 ±1.4	18.11, 20.4	97.26%	92.36 – 102.43%
$AUC_{(0-t)}$ (h*pg /mL)	6421.11 ±1.45	6569.33 ±1.43	6445.47 ±1.41	12.69, 13.28	98.91%	95.37 – 102.57%
$AUC_{(0-\infty)}$ (h* pg/mL)	6803.79 ±1.43	6920.45 ±1.41	6814.38 ±1.39	12.22, 12.9	99.28%	95.86 – 102.83%
$AUC_{(0-72)}$ (h*pg/mL)	6635.6 ±1.43	6754.7 ±1.41	6634.04 ±1.39	-	NA	NA
t_{max} (h)	1 (0.5–2.5)	1 (0.5–2.5)	1 (0.5–3.5)	-	NA	NA
$t_{½}$ (h)	13.82±1.2	13.7±1.2	14.18±1.18	-	NA	NA

*Values are geometric means ± geometric SD, except for t_{max}: median (range); *GMR= geometric means ratio; NA: Not applicable; FDC: Nebivolol Ramipril 5/10mg FDC; EC1: Nebivolol 5 mg +Ramipril 10 mg 1st EC intake; EC2: Nebivolol 5 mg +Ramipril 10 mg 2nd EC intake*

The Test/Reference geometric means ratio (GMR) was very close to 100% for Nebivolol C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. In addition, the 90% CI of the Test/Reference GMR fell within the pre-specified 80.00-125.00% limits for the 3 PK parameters, confirming a bioequivalent rate and extent of Nebivolol absorption between the FDC (Test) and the EC (Reference) formulations. Median t_{max} and mean $t_{1/2}$ values were 1 h and approximately 14 h, respectively, for both investigational products.

Main **Ramipril** plasma PK parameters and results of the bioequivalence test between FDC and EC are summarised in the following table:

PK parameter	**FDC**	**EC1**	**EC2**	**Overall intra-subject CV%, intra-subject CV% within Reference**	**GMR***	**90%CI**
C_{max} (pg/mL)	22060.45 ±1.71	21015.34 ±1.68	19334.28 ±1.82	30.75, 33.66	110.12%	100.99 – 120.07%
$AUC_{(0-t)}$ (h*pg /mL)	16912.22 ±1.65	16553.27 ±1.6	15295.55 ±1.62	16, 18.3	106.66%	101.89 – 111.66%
$AUC_{(0-\infty)}$ (h* pg/mL)	17433.41 ±1.65	17161.96 ±1.61	15724.99 ±1.61	15.99, 18.35	106.53%	101.76 – 111.51%
t_{max} (h)	0.5 (0.25–1.25)	0.5 (0.25–2)	0.5 (0.25–1.5)	-	NA	NA
$t_{½}$ (h)	1.08±2.21	1.23±2.25	0.92±1.96	-	NA	NA

Notes as above

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Results:

Pharmacokinetic primary and secondary endpoints results, continued

The Test/Reference GMR corresponded to approximately 110% and 107% for Ramipril C_{max} and AUC, respectively, indicating a slightly higher rate and extent of Ramipril absorption with FDC as compared to EC. Notably, the GMR was included in the 80.00–125.00% range, as requested by the EMA guideline on the investigation of bioequivalence as one of the conditions for BE conclusion for HVDs. In addition, the 90% CIs of the Test/Reference GMR were within the 77.96-128.27% enlarged acceptance range for C_{max} and the pre-specified 80.00-125.00% limits for $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. Notably C_{max} 90% CI was also within the 80.00-125.00% range specified by the EMA guideline for not highly variable drugs.

Exploratory pharmacokinetic endpoints results

Main **Ramiprilat** plasma PK parameters and results of the bioequivalence test between FDC and EC are summarised in the following table:

PK parameter	FDC	EC1	EC2	Overall intra-subject CV%, intra-subject CV% within Reference	GMR*	90%CI
C_{max} (pg/mL)	32197.61 ±1.72	29832.85 ±1.72	32208.6 ±1.6	16.75, 14.98	103.87%	98.92 – 109.07%
$AUC_{(0-t)}$ (h*pg /mL)	268963.6 ±1.34	253140.69 ±1.33	273821.03 ±1.26	8.14, 7.17	102.16%	99.75 – 104.63%
$AUC_{(0-\infty)}$ (h*pg pg/mL)	338536.78 ±1.32	317868.83 ±1.27	355582.74 ±1.29	10.53, 10.26	100.7%	97.64 – 103.85%
$AUC_{(0-72)}$ (h*pg/mL)	268961.68 ±1.34	253137.73 ±1.33	273818.63 ±1.26	-	NA	NA
t_{max} (h)	2 (1 – 3.5)	2 (1.25 – 4)	2 (1 – 4)	-	NA	NA
$t_{½}$ (h)	42.47±1.72	41.22±1.69	46.17±1.72	-	NA	NA

Notes as above

The Test/Reference GMR was very close to 100% for Ramiprilat C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. In addition, the 90% CIs of the Test/Reference GMR fell entirely within the pre-specified 80.00-125.00% limits for the 3 PK parameters, also confirming a bioequivalent rate and extent of Ramiprilat exposure between the FDC (Test) and the EC (Reference) formulations. Median t_{max} (2 h) was the same for the 2 investigational products, whereas mean $t_{1/2}$ values (geometric means) ranged from approximately 41 to approximately 46 h.

Safety results:

Overall, 38 TEAEs were experienced by 22 (40.74%) subjects during the study: 23 TEAEs were experienced by 13 (24.07%) subjects with the Reference product (EC) administered in two study periods, and 15 TEAEs by 13 (24.07%) subjects with the Test product (FDC). All reported TEAEs were of mild or moderate intensity.
Twenty-nine (29) of the reported TEAEs (18 TEAEs with EC and 11 TEAEs with FDC) were deemed related to the study treatment. The most reported treatment-related AEs (ADRs) overall were headache [4 (7.41%) subjects with EC and 5 (9.26%) subjects with FDC] followed by dizziness [3 (5.56%) subjects with EC and 2 (3.7%) subjects with FDC] and diarrhoea [one (1.85%) subject with both EC and FDC]. All the other ADRs were reported by one subject each, either with EC (vision blurred, nausea, retching, arthralgia, back pain, dysgeusia, hypotension) or with FDC (dyspepsia, myalgia).

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Safety results:

No SAEs or other significant TEAEs occurred. Two TEAEs reported during the FDC treatment session as not related to study treatment, i.e. second degree atrioventricular block and acarodermatitis, led to study withdrawal of the two affected subjects.

Clinical laboratory test results were in general within normal range or judged not clinically significant by the Investigator. However, a clinically significant out of range value (low Haemoglobin value) was observed for one subject. These clinically significant abnormalities were reported as a TEAE (anemia) unlikely related to study treatment, were transitory in nature and did not give rise to any safety concern.

Most ECG parameters were either within their normal range or considered not clinically significant by the Investigator, except for the "second degree atrioventricular block", which was reported by the Investigator as a TEAE of mild severity not related to study treatment (see above).

Vital signs results were either normal or not clinically relevant, except for one subject who experienced significant low blood pressure at 6 h post-dose in PK session 1. At the following assessment time (12 h post-dose), blood pressure for this subject was still abnormal but not clinically significant. The abnormal blood pressure findings for this subject were reported as a TEAE (PT: hypotension), related to the study treatment, and of moderate severity at onset, shortly improving to mild severity in four minutes.

Conclusions:

Bioequivalence between Nebivolol/Ramipril 5/10 mg FDC (Test) and Nebivolol 5 mg plus Ramipril 10 mg EC (Reference) was fully demonstrated in terms of rate and extent of absorption for both Nebivolol and Ramipril, according to the requirements of the current EMA guideline for bioequivalence studies (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **, 20JAN10). In fact, the 90% CIs of the ratios of geometric means fell entirely within the pre-specified acceptance limits of 80.00-125.00% for Nebivolol C_{max} and $AUC_{(0-t)}$ and for Ramipril $AUC_{(0-t)}$. Notably, for Ramipril C_{max}, the GMR was within the 80.00-125.00% acceptance range and its 90% CIs were within both the calculated enlarged acceptance limits of 77.96-128.27% and the 80.00-125.00% acceptance range.

The exploratory PK analysis on Ramiprilat, the main active metabolite of Ramipril, also confirmed the bioequivalence between Test and Reference formulations.

The study showed a comparable safety profile of NEB/RAM 5/10 mg FDC vs. NEB 5 mg + RAM 10 mg EC, with a low incidence of TEAEs observed both with the Test and the Reference formulations, and which resolved or were resolving by study end.

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