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Bioequivalence (amount of the product absorbed and distributed in the organism, as well as the speed of the processes) of two active products (nebivolol and ramipril) after administration to healthy subjects as fixed (in a single tablet) and extemporaneous (two tablets administered together) combination

Submission date 23/08/2024	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 16/09/2024	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 10/09/2024	**Condition category** Other	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims

Nebivolol and ramipril have been on the market for about three decades. Nebivolol has been evaluated for the treatment of hypertension (high blood pressure), both alone and in combination with other classes of antihypertensive drugs. The approval of nebivolol for the treatment of hypertension was based on evidence of its effectiveness and safety in three large dose-ranging studies in adults with hypertension. Results from each study consistently showed significant reductions in blood pressure with nebivolol doses ranging from 5 to 40 mg daily. Large-scale studies have demonstrated that the antihypertensive effectiveness of ramipril is comparable to that of enalapril, captopril, lisinopril and atenolol. In placebo-controlled studies, once daily administration of ramipril 2.5 to 20 mg for 3 months achieved target blood pressure in over 50% of diabetic patients with mild to moderate hypertension, without adversely affecting plasma glucose and lipid levels. Moreover, the drug significantly decreased the urinary albumin excretion rate in diabetic patients with nephropathy (kidney disease).
This study aims to demonstrate in healthy volunteers the bioequivalence (amount of the product absorbed and distributed in the organism, as well as the speed of the processes) of the fixed-dose combination (FDC: a single tablet containing both nebivolol and ramipril) versus already marketed single components in extemporaneous combinations (EC: separate tablets), as they are commonly used in the ordinary clinical setting to treat hypertensive patients.

Who can participate?

Healthy male and female volunteers aged 18-60 years

What does the study involve?
All the participants will undergo three sessions, each one separated by a minimum of a 14-day wash-out period between each dosing. Each session includes the administration of the Test or Reference formulation in a fasting condition as randomly allocated and blood sampling at predefined timepoints up to 72 hours post-dose. In detail, during each session, each volunteer will take one NEB/RAM 5/10 mg FDC film-coated tablet (Test) or the corresponding extemporaneous combination of the two components, i.e. NEB 5 mg + RAM 10 mg EC (Reference). The sequence of treatments in the study sessions will follow the randomization list. The test and the reference formulation will be taken as single doses in fasting condition, 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 extemporaneous co-administration of NEB 5 mg and RAM 10 mg should be taken almost simultaneously, i.e. one immediately after the other.

What are the possible benefits and risks of participating?
No direct benefit is expected for the participants. No significant risks are expected following one single oral administration of the Test or Reference treatment since the study will be carried out in healthy volunteers aged between 18 – 60 years old who have successfully passed the Screening evaluating their well-being status based on medical history, physical examination, clinical and laboratory parameters.
A significant hypotensive (low blood pressure) effect is not expected following the administration of a single dose of nebivolol 5 mg and ramipril 10 mg; however, as mitigation action volunteers are eligible to participate in the study if their systolic/diastolic blood pressure and pulse rate is ≥90/60 mmHg with a pulse rate of 50 beats/min, and they have no history of orthostatic hypotension. In addition, the 'single dose' administration is secured by a minimum 14-day washout phase between the two study periods to avoid any carry-over effect of the previous dose or/and any presence of the drugs. The washout phase duration covers 5 elimination half-lives of the tested drug with the longest half-life (t1/2 of 12 h considered for nebivolol). Genotyping of eligible participants also excludes poor and intermediate CYP2D6 metabolizers, thus minimizing the risk of overexposure.
To note that subjects will be resident in the Clinical Unit for 72 hours after the single administration of the study treatment; therefore, they will be monitored for any possible adverse drug reaction, including those that are reported in the approved SmPC of each drug prior to leaving the Unit. Monitoring of cardiovascular parameters (blood pressure, pulse rate and ECG) are also included at different timepoints after treatment up to 24 hours and at the end of study visit.
No risk is anticipated as a consequence of the study procedures per se, being those usually applied in pharmacokinetic studies and mainly consisting of repeated blood sampling. The total blood volume which will be withdrawn for the tests is standard and acceptable, taking the study population (healthy volunteers) and the duration of the study into account. In addition, cardiovascular safety parameters (blood pressure and ECG) and physical signs will be assessed at predefined time points after treatment administration to monitor any change and avoid further exposure of the subjects to study treatments/study procedures in case of the occurrence of clinically significant findings.

Where is the study run from?
Menarini Ricerche SpA (Italy)

When is the study starting and how long is it expected to run for?
March 2023 to October 2023

Who is funding the study?
Menarini Ricerche SpA (Italy)

Who is the main contact?
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Public, Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers

NEB-RAM-01 - CRO-PK-23-364

Study information

Scientific Title
Bioequivalence of nebivolol and ramipril following their oral co-administration as fixed and extemporaneous combination in healthy subjects

Acronym
NEB-RAM combination

Study objectives
Evaluation of the bioequivalence of the nebivolol/ramipril 5/10 mg film-coated fixed-dose combination tablet (NEB/RAM 5/10 mg FDC) - Test - versus nebivolol 5 mg tablet and ramipril 10 mg tablet given as extemporaneous combination (NEB 5 mg + RAM 10 mg EC) - Reference

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 02/06/2023, Cantonal Ethics Committee Canton Ticino (Health Office, Via Orico 5, Bellinzona, 6501, Switzerland; +41 (0)91 8143057; dss-ce@ti.ch), ref: 2023 00618 CE 4332

Study design
Open-label randomized two-treatment three-period three-sequence single-dose partial replicate cross-over design

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Phase I study in healthy volunteers of both sexes

Interventions
The study consists of:
1. Screening (to be performed within 4 weeks prior to the 1st PK study session), for the evaluation of the volunteer's eligibility.

2. Three PK study sessions, each one separated by a minimum of a 14-day wash-out period between each dosing. Each PK session includes the administration of Test or Reference formulation in fasting condition as per randomization sequence and blood sampling for PK plasma assessment at predefined time points up to 72 hours (h) post-dose. In detail, during each PK session, each subject will take 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). The sequence of treatments in the three PK study sessions will follow the randomization list. The test and the reference formulation will be taken as single doses in fasting condition, 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 extemporaneous co-administration of NEB 5 mg and RAM 10 mg should be taken almost simultaneously, i.e. one immediately after the other.
3. End of Study Visit (10-12 days after the last treatment administration).

The study will be performed according to an open design with a treatment sequence allocated to each subject according to the randomisation list; no blinding technique will be used. Each randomised subject will be allocated to a sequence (Sequence A, Sequence B or Sequence C) of treatment administrations in the three study periods (Periods 1, 2 and 3) according to a computer-generated randomisation list. The Clinical Sciences Department of Menarini Group will be responsible for generating the randomisation list. The list should be kept at the site. As soon as the subject's eligibility to be randomized is confirmed, the subject will be assigned to the lowest randomisation number available in the list.

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

Intervention Type
Drug

Pharmaceutical study type(s)
Bioequivalence

Phase
Phase I

Drug/device/biological/vaccine name(s)
Nebivolol, ramipril

Primary outcome measure
Area Under the plasma concentration-time Curve (AUC) from time zero to the last quantifiable time point (AUC(0-t)) and maximum plasma concentration (Cmax) of NEB and RAM when administered as FDC tablet (Test) and as EC tablets (Reference). The concentrations of NEB and RAM in plasma samples are determined using a fully validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method by the analytical laboratory Anapharm, Spain at different timepoints from baseline up to 72 h post-dose

Secondary outcome measures
1. Relevant secondary standard pharmacokinetic parameters of NEB and RAM such as AUC from time zero to infinity (AUC(0-∞)), AUC from time zero to 72h (AUC(0-72)) for NEB only, plasma terminal half-life (t1/2), terminal elimination rate constant (λz), residual area (%AUCextrap) and time to maximum plasma concentration (tmax) when NEB and RAM are administered as Test and

Reference formulations. The concentrations of NEB and RAM in plasma samples are determined using a fully validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method by the analytical laboratory Anapharm, Spain at different timepoints from baseline up to 72 h post-dose
2. Safety and tolerability of the study treatments are evaluated by collecting the adverse events during the whole study, by measuring vital signs (blood pressure and heart rate) and registering an ECG at screening, baseline, during the study and at the final visit, by performing a physical examination at screening, baseline and final visit, and by performing laboratory tests on blood and urine at the screening and final visits.

Overall study start date
01/03/2023

Completion date
16/10/2023

Eligibility

Key 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 and 30 kg/m2, 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 must be using at least one of the following reliable methods of contraception:
6.1. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
6.2. 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
6.3. A male sexual partner who agrees to use a male condom with spermicide
6.4. A sterile sexual partner
6.5. True abstinence. 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:
7.1. 12 months of spontaneous amenorrhea or
7.2. 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or
7.3. 6 weeks documented postsurgical bilateral oophorectomy with or without hysterectomy will be admitted
8. Male participants with a partner of childbearing potential must agree to use a barrier method (condom with spermicidal cream) when sexually active while participating in the study, unless they are 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

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
Both

Target number of participants
54

Total final enrolment
54

Key exclusion criteria
1. 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 mmHg in SBP or a drop of at least 10 mmHg 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 judgement.
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 a 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).
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 the 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 are not using any of the highly effective contraceptive methods (see inclusion criterion 6).
14. Breastfeeding and pregnant females as per positive β-HCG (Beta-subunit Of Human Chorionic Gonadotropin) results at Screening and at 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 is 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 or food supplement in the last 14 days prior to the dosing.
17. Receiving concomitant treatment with other investigational medicinal product (IMP) or who have 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 follows the last visit of the previous study and the first day of the present study (or 5 half-lives of IMP, whichever is longer) before Screening.
18. Poor, intermediate and ultra-rapid metabolizers for CYP2D6 based on the genotype.
19. Any person who, in the judgement of the Investigator, is 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 cannot be contacted in case of emergency.
21. Vulnerable, defined as a 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. A 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 has had clinical signs and symptoms consistent with coronavirus 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.

Date of first enrolment
26/06/2023

Date of final enrolment
25/08/2023

Locations

Countries of recruitment
Switzerland

Study participating centre
CROSS Research S.A. - Phase I Unit
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Sponsor information

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Sponsor type
Industry

Website
https://www.menarini.it

ROR
https://ror.org/02h1wg091

Funder(s)

Funder type
Industry

Funder Name
Menarini Group

Alternative Name(s)
A. Menarini Industrie Farmaceutiche Riunite Srl, Menarini Ricerche SpA, Menarini Ricerche S.p.A.

Funding Body Type
Private sector organisation

Funding Body Subtype

For-profit companies (industry)

Location
Italy

Results and Publications

Publication and dissemination plan
Planned publication in a peer-reviewed journal.

Intention to publish date
31/12/2025

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be available upon request from Daniela Menichini (dmenichini@menarini-ricerche.it). All details regarding the type of data that will be shared, access criteria, for what types of analysis and other details or comments, please directly refer to Daniela Menichini.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other files	Informed consent form version 2.0	24/05/2023	10/09/2024	No	No
Protocol file	version 1.0	28/03/2023	10/09/2024	No	No