MENARINI RICERCHE

CLINICAL TRIAL PROTOCOL

FINAL VERSION 1.0, 28 March 2023

BIOEQUIVALENCE OF NEBIVOLOL AND RAMIPRIL FOLLOWING THEIR ORAL CO-ADMINISTRATION AS FIXED AND EXTEMPORANEOUS COMBINATION IN HEALTHY SUBJECTS

AN OPEN-LABEL, RANDOMIZED, TWO TREATMENT, THREE PERIOD, THREE SEQUENCE, SINGLE DOSE, PARTIAL REPLICATE CROSS-OVER STUDY

Trial Code	NEB-RAM-01
Investigational Medicinal Product	Nebivolol/Ramipril 5/10 mg Fixed Dose Combination (FDC); Nebivolol 5 mg + Ramipril 10 mg as extemporaneous combination (EC).
Development phase of study	Phase I, Bioequivalence Study
Study type and design	Open label, randomized, two-treatment, three-period, three-sequence, single-dose, partial replicate cross-over study.
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

CRO	CROSS RESEARCH SA Massimo Assandri, *Administrative Manager* via F. A. Giorgioli 14, CH-6864, Arzo (TI), Switzerland

1 SIGNATURES

The signatories have read the clinical trial protocol titled ***"Bioequivalence of Nebivolol and Ramipril following their oral co-administration as fixed and extemporaneous combination in healthy subjects." - Final Version 1.0, dated 28 March 2023*** - carefully and agree to adhere to its provisions. Changes to the protocol have to be stated by the sponsor in amendments to the clinical trial protocol which, if they are substantial, have to be authorised by the Competent Authorities and Ethics Committees before translating them into action.

Sponsor's Representative	**Signature**	**Date**
Dr. Angela Capriati Global Director of Clinical Sciences Menarini Ricerche S.p.A.	CAPRIATI ANGELA 2023.03.29 15:56:57 CN=CAPRIATI ANGELA C=IT 2.5.4.4=CAPRIATI 2.5.4.42=ANGELA	.....
Principal Investigator	**Signature**	**Date**
Dr. Milko Radicioni CROSS Research SA, Phase I Unit, Switzerland	.....	29 MARCH 2023 .....

PRINCIPAL INVESTIGATOR'S STATEMENT

a) Clinical Statement

My signature below documents my agreement with the contents of this clinical trial protocol titled ***"Bioequivalence of Nebivolol and Ramipril following their oral co-administration as fixed and extemporaneous combination in healthy subjects." - Final Version 1.0, dated 28 March 2023 -*** with regard to the execution of the study and the required documentation / data collection. I agree to comply with this clinical trial protocol in its entirety and with the ICH guidelines for Good Clinical Practice (GCP) and the applicable local law requirements.

b) Anti-Corruption Statement

I agree to - I will and I will cause any of my collaborators to - perform any activity in accordance with the principles any international anti-corruption legislations, e.g. OECD Convention on Combating Bribery of Foreign Public Officials in International Business Transactions, UK Bribery Act and US Foreign Corrupt Practices Act, including Italian Legislative Decree 231/2001. In particular, along the performance of the study, I will not - and I will cause any of my collaborators not to - directly or indirectly offer, pay, give, or promise to pay or give or receive any payment or gift of any money or thing of value to or from any government officer to influence any acts or decisions or to induce such officer to use its influence to effect or influence the decision of the relevant government body or any other decision maker. I accept to promptly inform the Sponsor in writing in case of violations of or deviations from any of the above prescriptions in the conduct of the study and I acknowledge and accept Sponsor's rights to conduct audits in order to verify compliance with the above during or in connection with the performance of the study. I agree and accept that a violation of any of the above prescriptions may result in the termination of the research activities of the site I work in and / or the entire study Any episode of non-compliance will be documented.

Principal Investigator	**Signature**	**Date**
Dr. Milko Radicioni, MD PhD CROSS Research SA, Phase I Unit, Switzerland	.....	29 MARCH 2023

2 PROTOCOL SYNOPSIS

Study Title **Nick name / Acronym** **Sponsor Study Code**	Bioequivalence of Nebivolol and Ramipril following their oral co-administration as fixed and extemporaneous combination in healthy subjects. NEB-RAM-01
Phase	Phase I, Bioequivalence study.
Indication	Not applicable, healthy male and female subjects.
No. of sites & countries	Single centre, Switzerland
Investigational Medicinal Product, **Reference therapy,** **Treatment regimen**	*Test Formulation:* Nebivolol/Ramipril 5/10 mg film-coated Fixed Dose Combination tablet (hereinafter reported as NEB/RAM 5/10 mg FDC). *Reference Formulation:* Nebivolol 5 mg tablet and Ramipril 10 mg tablet given as extemporaneous combination (hereinafter reported as NEB 5 mg + RAM 10 mg EC). *Treatment regimen:* Single oral dose of Test and Reference formulations.
Study Type and Design (see also § 2.1.)	The study will run according to an open label, randomized, two treatment, three period, three sequence, single dose partial replicate cross-over design.
Primary Objective	Evaluation of the bioequivalence of the NEB/RAM 5/10 mg FDC (Test) versus NEB 5 mg + RAM 10 mg EC (Reference)
Secondary Objective/s	Evaluate 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.
Pharmacokinetic (PK) Endpoints	*Primary PK parameters:* Area Under the plasma concentration-time Curve (AUC) from time zero to the last quantifiable time point ($AUC_{(0-t)}$) and maximum plasma concentration (C_{max}) of NEB and RAM when administered as FDC tablet (Test) and as EC tablets (Reference). *Secondary PK parameters:* 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 (λz), residual area ($\%AUC_{extrap}$) and time to maximum plasma concentration (t_{max}) when NEB and RAM are administered as Test and Reference formulations. *Exploratory PK parameters:* AUC from time zero to 72h ($AUC_{(0-72)}$), t_{max}, λz, $t_{1/2}$ and C_{max} of Ramiprilat when NEB and RAM are administered as Test and Reference formulations.

	Other PK parameters for all the analytes can 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).
Study Population: Subjects characteristics Number of Subjects	The study population, aged 18 to 60 years, will include a total of 54 healthy male and female subjects who will receive single doses of Test and Reference formulations according to the assigned randomized sequence A, B or C, as described in the schematic study design, § 2.1.
Study Duration	The study consists of: o *Screening* (to be performed within 4 weeks prior to the 1st PK study session), for the evaluation of subject's eligibility. o *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 (A-B-C) and blood sampling for PK plasma assessment at predefined time points up to 72 hours (h) post-dose. o *End of Study Visit* (10-12 days after the last treatment administration). The clinical phase of the study is planned to run in 2Q 2023 and end in 4Q 2023. The trial will end with the last visit of the last subject (LSLV).
Inclusion criteria	To be eligible for this study, EACH of the following criteria must be satisfied: 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 must be using at least one of the following reliable methods of contraception: o Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit o 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 o A male sexual partner who agrees to use a male condom with spermicide o A sterile sexual partner

	○ 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: ○ 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 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.
Exclusion criteria	To be eligible for this study, NONE of the following criteria must be satisfied: 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 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 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. Breast-feeding 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, food supplement in the last 14 days prior to the dosing. 17. Subjects 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 subject 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 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 has 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.
Study procedures and PK and Safety assessments (see also flow chart in § 2.2)	As part of the COVID-19 risk mitigation, a RT-PCR or a rapid antigen test will be performed at screening and at each subject's Admission in the clinical unit. In case a subject becomes positive for SARS-CoV-2 infection after being randomized, a 2-week window will be allowed for recovery. By the end of this period, provided that the subject has recovered from the infection (i.e. negative test at the admission to the site), he/she may resume the study participation if the investigator deems it appropriate. Otherwise the subject will be withdrawn from the study and considered as a drop out. **Screening** *(within 4 weeks prior to 1st PK study session)*

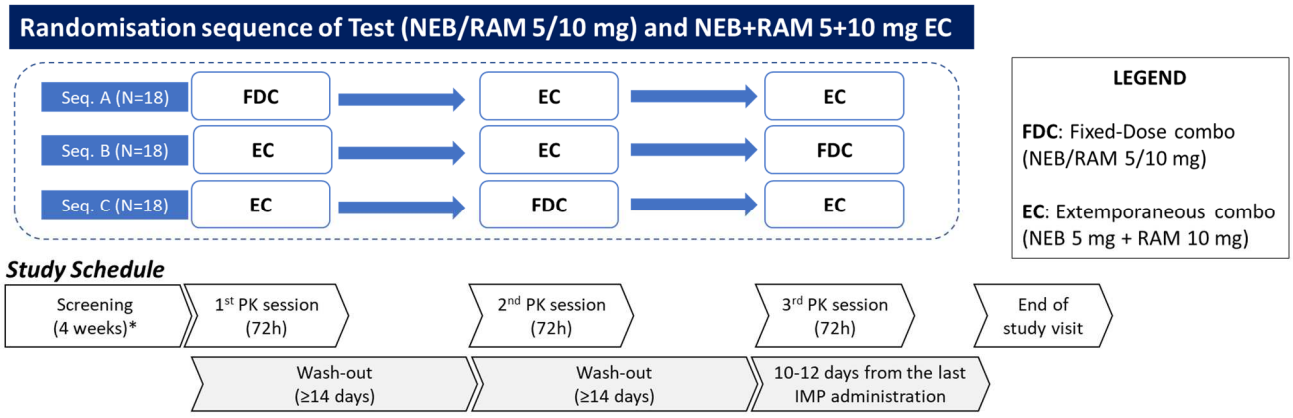
	Once a written informed consent is properly executed, the Screening procedures as described in the flow chart (see § 2.2) will be performed across different visits, as needed. NOTE 1: Genetic evaluation of CYP2D6 activity is not required if previous results are made available to the Investigator. NOTE 2: re-screening to evaluate study eligibility is allowed provided that the subject has not already been randomized to the assigned treatment. **PK study sessions** (*three sessions, each separated by a minimum of 14-day wash-out period between each dosing*). Study procedures to be applied to each PK study session are reported in the study flowchart (see § 2.2). NOTE: Pre-dose study procedures might be completed on Day-1 (the day before the PK session, when subjects start their residence at the study site), the only exception being baseline vital signs, ECG and PK sample collection that should be done close to dosing. ***In the Clinical Unit, Residence*** of subjects will start from the evening of the day prior to each PK study session until 72-h post dosing, i.e. after the last PK sampling and study procedures have been completed. Subjects must abstain from extraneous exercise during residence in the Unit. ***Dosing*** will start after baseline (prior to dosing) procedures are completed, with one of the following two treatments being administered orally in the morning, in fasting condition with 240 mL of still water as per randomisation sequence (see §2.1): ● NEB/RAM 5/10 mg FDC; ● NEB 5 mg + RAM 10 mg EC. NOTE: The two tablets of the extemporaneous combination should be taken almost simultaneously, i.e. one immediately after the other. Intake time will be recorded for each drug. Subjects will be required to fast for at least 10 h overnight prior to each morning dose. The fast will be broken approximately 4 h after dosing with a light standard lunch. Subjects will not be allowed to drink any water 1 h before and 1 h after the dosing, with the exception of water foreseen for treatment administration. In order to maintain adequate hydration, the subjects will be encouraged to drink at least 180 mL of still mineral water every 2 h for 5 h post-dose, starting at 1 h post-dose.

	A baseline blood sample (T+0') of 8 mL (5 mL for nebivolol and 3 mL for ramipril and ramiprilat) will be drawn just before dosing for PK plasma assay. ***After dosing***, blood sampling (8 mL, 5 mL for nebivolol and 3 mL for ramipril and ramiprilat, each), for PK plasma assay, will be performed at the following predefined time points: ● **Nebivolol and Ramiprilat PK samples**: T+5', T+15', T+30', T+45', T+1h, T+1.25h, T+1.5h, T+2h, T+2.5h, T+3h; T+3.5h, T+4h, T+6h, T+8h, T+10h, T+12h, T+24h, T+48h and T+72h post dose. ● **Ramipril PK samples**: T+5', T+15', T+30', T+45', T+1h, T+1.25h, T+1.5h, T+2h, T+2.5h, T+3h; T+3.5h, T+4h, T+6h, T+8h, T+10h, T+12h, and T+24h post dose. ***During Residence and before discharge from the Unit***, Recording of any AE that occurred during all the experimental phase and of all the concomitant medications taken, if any. **End of Study Visit** (10-12 *days after last treatment administration*) Examinations or tests to be performed during this visit are reported in the flowchart (see § 2.2) In case of study discontinuation, as far as possible and with the subject's consent, the End of Study Visit (EOS) assessments should be performed.
Determination of Sample size	The sample of 42 subjects evaluable for the PK analysis (14 subjects per each of the sequences A, B and C) is considered adequate for testing the bioequivalence between NEB/RAM 5/10 mg FDC (Test formulation) and NEB 5mg + RAM 10 mg EC (Reference formulation) at 5% (one side) level of significance with a power higher than 80% based upon a Test versus Reference ratio of 0.95 and 1.05 and an intra-subject coefficient of variation of a maximum of 36.2%. [(1), (2)] In order to account for approximately a 22% of potential dropouts during the clinical phase and exclusions from the PK population, twelve extra subjects will be included into the study and a total number of 54 subjects will be randomized.
Analysis populations	*Safety population:* All subjects receiving at least one administration of the IMP. *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 formulation, and who did not experience major protocol violations or events impacting the PK results.

Statistical Analysis	The PK analyses will be run on the PK population. All PK parameters and variables will be summarized by descriptive statistics that will include: 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. Individual plasma concentration versus time profiles (linear and semi-log scales) for Nebivolol, Ramipril and Ramiprilat will be graphically displayed by subject and treatment and overall, as appropriate. Pharmacokinetic parameters for Nebivolol, Ramipril and Ramiprilat will be derived from individual measured concentrations by means of non-compartmental analysis (NCA) using Phoenix™ WinNonlin® software, version 8.3.5 or higher (Pharsight Corp., Mountain View, California). PK parameters will be determined following partial replicated administration of Test and Reference formulations, as appropriate, by period. This means that there will be 2 PK profiles for EC, one PK profile for FDC. ***Analysis of 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 will be analysed using a mixed effect model including sequence, period, formulation, and subject within sequence as fixed effects and taking into account the partial replicate design. Estimates of the mean difference (Test formulation – Reference formulation) and corresponding 90% CIs will be obtained from the model for each analyte. The mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of geometric means (Test formulation/Reference formulation) and 90% corresponding CIs. Bioequivalence will 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 fall wholly within the bioequivalence acceptance range (80.00% to 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. 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} can be widened to a maximum of 69.84 – 143.19% in case the observed

	intra-subject CV% for the reference is confirmed as > 30%, according to the formula: $[U, L] = \exp[\pm k \cdot sWR]$ 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 $\sqrt{ln(CV^2+1)}$. The geometric mean ratio 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 will be compared when administered as FDC tablet vs. EC: - $AUC_{(0-\infty)}$ will be analysed similarly to $AUC_{(0-t)}$. - Other PK parameters will be summarized descriptively. ***Analysis of Exploratory PK variables:*** Exploratory PK parameters will be summarized descriptively. The bioequivalence testing may be required for Ramiprilat as well in case of inconclusive results of the BE based on Ramipril. ***Analysis of Safety variables:*** Safety variables relative to the safety population (all subjects receiving at least one dose of the IMP) will be summarized by descriptive statistics only.

2.1 Schematic study design



* Screening ≤ 4 weeks for genotyping.

2.2 Study Flow Chart

Procedures	**Screening**	**1st, 2nd and 3rd PK session (separated by a minimum 14-day wash-out period between dosing)**																				**End of Study visit**
	≤ 4 weeks prior to 1st PK Session*	T+0[1, #]	T+5'	T+15'	T+30'	T+ 45'	T+ 1h	T+ 1.25h	T+ 1.5h	T+ 2h	T+ 2.5h	T+ 3h	T+ 3.5h	T+ 4h	T+ 6h	T+ 8h	T+ 10h	T+ 12h	T+ 24h	T+ 48h	T+ 72h	10-12 days after last dose
Informed consent	X																					
Incl./Excl. criteria	X	X																				
Demographic data	X																					
Medical history	X																					
Genotyping for CYP2D6	X																					
Physical examination	X[2]	X																				X
Haematology, biochemistry, Urinalysis	X																					X
Pregnancy test (β-HCG)[9]	X	X																				X
Serology (HIV, HBV, HCV)	X																					
Drugs of abuse [3] + alcohol test + cotinine urine test	X	X																				
Vital signs + 12-lead ECG[4]	X	X							X						X			X	X			X
Check of study restrictions		X																				
Randomisation		X[5]																				
Study Treatment Administration [6]		X																				
Nebivolol and Ramiprilat PK sample collection [7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ramipril PK sample collection[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Prior and Concomitant medications	X		→
AE recording	X[8]	X[8]	→
Residence in Phase I unit [&]		→	

[1] T+0 corresponds to time of Study Treatment Administration, all other assessments at this time point to be completed prior to dosing.
[2] At Screening, physical examination also includes body weight and height for BMI calculation.
[3] Drugs of abuse urine test 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).
[4] Vital signs include supine SBP and DBP, PR, RR, Frontal Body Temperature (°C). At Screening only, orthostatic BP is also included. Prior to dosing, Vital signs and ECG should be performed within 1 hour before dosing; Post-dose assessments are limited to SBP, DBP, PR and ECG to be performed within 30 minutes before the PK sampling.
[5] Prior to dosing of the 1st PK session only.
[6] One out of two study treatments as per randomized sequence.
[7] A time window for blood sample collection is allowed as follows: ± 2 minutes for blood sampling from T+15' to T+4h; ± 5 minutes for blood sampling from T+5h to T+24h; ± 30 minutes for blood sampling at T+48h and T+72h.
[8] At screening and pre-dose (for 1st PK session only), to record also any clinical event, not associated to a drug intake, prior to IMP administration that occurs for the first time or worsens after signing the informed consent
[9] On serum at screening and on urine at each Admission to the clinical centre

[*] NOTE: Screening procedures shall start within 4 weeks prior to 1st PK study session (4 weeks also for genotyping). ALL screening procedures should be completed, and results made available prior to randomization/start of the first PK study session.
[#] NOTE: T+0 study procedures might be completed the day prior to dosing, the exception being baseline vital signs, ECG and PK sampling that should be done immediately before dosing.
[$] NOTE: re-Screening is allowed provided that the subject has not already been randomized.
[&] NOTE: Residence starts the evening before dosing and ends 72 h post dosing (each PK session). Subjects will be tested for SARS-CoV-2 infection by PCR/rapid antigen tests at screening and at each Admission to the Phase I Unit

3 INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE

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4.2 List of abbreviations and definition of terms

ABBREVIATION	DEFINITION
ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area Under the plasma Concentration time-curve
$AUC_{(0-\infty)}$	Area Under the plasma Concentration time-curve from time 0 until infinity
$AUC_{(0-t)}$	Area Under the plasma Concentration time-curve from time 0 until the last quantifiable concentration
BLOQ	Below Limit Of Quantification
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CI	Confidence Interval
C_{last}	Last quantifiable plasma drug Concentration
C_{max}	maximum plasma drug Concentration
Covid-19	Corona Virus Disease 19
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Clinical Trial
CTM	Clinical Trial Medication
CV%	Coefficient of Variation
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DPO	Data Protection Officer
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End of Study Visit
EC	Extemporaneous Combination

FDC	Fixed-Dose Combination
GCP	Good Clinical Practice
HbcAb	Hepatitis B core antigen
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
LLOQ	Lower Limit of Quantification
LSLV	Last Subject completing the Last Visit
MSC	Member States concerned
NSAE	Non-Serious Adverse Events
PCR	Polymerase chain reaction
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	Pulse Rate
RMS	Reporting Member State
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome - Coronavirus 2
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDSM	Study Drug Safety Manager
SDSU	Study Drug Safety Unit
SmPC	Summary of Product Characteristics
SOC	System Organ Class

SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TMF	Trial Master File
β-HCG	Beta-subunit of Human Chorionic Gonadotropin

5 ETHICAL AND LEGAL ASPECTS

5.1 General Aspects

This study will be carried out in compliance with the study protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki, International Council of Harmonisation – Good Clinical Practice (ICH-GCP) Guidelines, and the applicable local regulatory requirements.

The Sponsor has contracted the Contract Research Organisation CROSS Research S.A. (for details refer to the § 3) to perform some of the Sponsor's trial related duties and functions i.e., submission process to Competent Authority (CA) and Independent Ethical Committee (IEC), study management and monitoring activities, bioanalyses samples and non-compartmental PK analyses. The Sponsor will perform medical monitoring, data management, statistical analysis and medical writing. The ultimate responsibility for the quality and the integrity of the study resides with the Sponsor. The study will be conducted in agreement with Sponsor's, Site's and Contract Research Organisation's (CRO's) Standard Operating Procedures' (SOP) requirements as agreed.

5.2 Subject Information and Declaration of Consent

Before any study-related procedures may be performed, informed consent must be obtained from the subject by means of a signed declaration.

The Informed Consent Form (ICF) must be approved in the corresponding local language and in accordance with local laws and regulations by the IEC prior to being submitted to the subject.

Subjects will be given information and a fully comprehensive explanation in easily understandable terms of the study procedures, regarding the benefits, restrictions, discomforts, and risks in taking part in the study, the properties of the Investigational Medicinal Products (IMPs) and the method of assignment to treatments.

Subjects will also be informed about the measures taken to ensure their confidentiality according to the pertinent legislation. Subjects will be provided with information prepared in the local language, regarding the processing of personal data according to the Swiss Federal Law on Data Protection (Law 235.1 of 19 June 1992 and subsequent updates) and the European General Data Protection Regulation (GDPR, EU Regulation n 2016/679).

Subjects' will be given adequate time and opportunity to ask questions and understand all aspects of the study.
After being duly informed and interviewed by the Investigator, the subject freely has to date (including time) and sign the ICF before being enrolled into the study and before undergoing any study procedure. The Investigator must store the original of the signed ICF in the Investigator's File, and the subject will be provided with a copy. The process of obtaining the ICF has to be documented in the source documents.

If a protocol amendment would affect the terms of the ICF, it will be revised to reflect the protocol change and submitted to IEC for approval. The Investigator will ensure that this new consent form is signed by all subjects subsequently entered in the study and those currently in the study, before the changes take effect on their participation in the trial. Subjects who will not sign the new consent form need to be terminated from the study participation.

5.3 Subject Insurance

For subjects participating in the study, the Sponsor Menarini Ricerche S.p.A. has stipulated an insurance policy in accordance with local regulatory requirements.
Details on the insurance company, the insurance number and conditions will be made available to the subjects in the ICF and / or provided as a separate document, in accordance with national requirements.
A copy of the insurance certificate will be filed in the Investigator's File at the site and in the study's Trial Master File (TMF).

5.4 Documentation of Study-related Data and Record Retention

It is the responsibility of the Investigator to document all study-related data for each subject in the source documents and in an electronic case report form (eCRF). The investigator has to guarantee the accuracy of the documented data and has to comment on any missing or spurious data.

In addition to the eCRF the investigator will maintain adequate records that fully document the participation of the subject in the clinical study including the study assessments (subject source data documentation). Details on the source data documentation are provided in § 11.3. Requirements for record retention are specified in § 5.11.5.

Subject data (e.g. eCRFs, safety laboratory data) have to be archived for at least 10 years. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

No study documents should be destroyed without prior written agreement between Sponsor and Investigator. Should the Site/Investigator wish to move the study record to another location, he / she must notify the Sponsor in writing.

5.5 Confidentiality

By signing the study protocol, the investigator affirms that any information provided by the Sponsor will be maintained in confidence.

In order to maintain the subject's confidentiality, all data collected by the investigator will be recorded coded (pseudonymously) in the eCRF. Subject's data will be identified by a unique subject number defined as reported in § 11.1. The investigator agrees that within national regulatory restrictions and ethical considerations, representatives of the Sponsor, any regulatory agency, and IEC may consult study source documents in order to verify data in the eCRF. Subject medical records pertinent to the study will be reviewed by the study monitor to assure adequate source documentation, accuracy, and completeness of eCRFs. The review will be conducted in accordance with relevant SOPs and with strict adherence to professional standards of confidentiality, GCP, and the relevant data protection legislation.

5.6 Protocol / Protocol Modifications

The protocol must be read thoroughly by everybody whom the information therein concerns and the instructions must be exactly followed.

Changes in the study protocol will require a protocol amendment. Such amendments will be agreed upon and approved in writing by all signatories of the protocol. If amendments are substantial, i.e. they are likely to have an impact on the safety of the subjects, or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, the IEC and the CA, as applicable, in the participating countries have to approve these amendments before implementation.

Changes which have no significant impact on medical or scientific validity of the study will be agreed upon and approved in writing by all signatories of the protocol and the IEC and the CA will be notified of this protocol amendment.

5.7 Study Commencement

The study can commence at the study site only after all prerequisites are fulfilled according to ICH / GCP guidelines, any local regulatory requirements, and the Sponsor/Site/CRO's SOPs.

5.8 Subject's Safety

If any event related to the conduct of the study or the development of the IMP affects the safety of the study participants, the Sponsor and the investigator will take appropriate urgent safety measures to protect the subjects against any immediate hazard. The CAs and IEC will be informed forthwith about these new events and the measures taken.

5.9 Data Property / Publication Policy

All data generated in the study (e.g. eCRFs, the structured data files in the clinical database system, the results of the statistical evaluation, and medical interpretation as well as the final clinical study report) are the property of Menarini Ricerche S.p.A.

The results of the study may be published as scientific literature. Results may also be used in submissions to CAs. The conditions mentioned below are intended only to protect confidential commercial information (patents, etc.), and not to restrict publication.

All information concerning the IMP (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by Menarini Ricerche S.p.A. and not previously published) is considered confidential by Menarini Ricerche S.p.A. and will remain the sole property of Menarini Ricerche S.p.A. The investigator agrees not to use it for other purposes without written consent from Menarini Ricerche S.p.A.

Menarini Ricerche S.p.A. will use the information obtained in this clinical study in connection with the development of the IMP and therefore may disclose it to other investigators or concerned CAs in the European Union or in other countries. In order to allow for the use of information derived from this clinical study, the investigator has an obligation to provide Menarini Ricerche S.p.A. with complete test results and all data recorded during this study.

Prior to submitting the results of this study for publication or presentation, the investigator will allow Menarini Ricerche S.p.A. at least 60 days of time to review and comment upon the publication manuscript. Menarini Ricerche S.p.A. will provide any manuscript of the results of this study to the authors at least 30 days before submission for a complete review. In accordance with generally recognised principles of scientific collaboration, co-authorship with any Menarini Ricerche S.p.A. personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until Menarini Ricerche S.p.A. has reviewed / commented and agreed to any publication. Further details on the publication policy are defined in the site agreement.

5.10 Data Protection

5.10.1 General Principles on Personal Data Compliance

All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the confidentiality of records and of the personal data of the subjects shall remain protected in accordance with the applicable law on personal data protection such as the Swiss Federal Law on Data Protection (Law 235.1 of 19 June 1992 and subsequent updates), the EU General Data Protection Regulation 679/2016.
This section defines the appropriate technical and organisational measures that shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss as well as to assure the fulfilment of subjects' privacy rights.

5.10.2 Acknowledgement

The Site, the Principal investigator, the bioanalytical laboratory and the laboratory for routine safety analysis and genotyping, the CRO as well as their appointed staff and service providers acknowledge that:

a) the performance of the study will imply processing of sensitive personal data;

b) personal data processing is regulated by the applicable European (i.e. Swiss Federal Law on Data Protection (Law 235.1 of 19 June 1992 and subsequent updates), the EU General Data Protection Regulation 679/2016) and local laws (i.e. the laws of the country where the study is conducted) as well as by the Sponsor's national legislation. In particular, it is hereby acknowledged that being the Sponsor a company incorporated under Italian law, it has to mandatorily comply with Italian legal provisions on data protection: therefore, the Site, the Principal investigator, the bioanalytical laboratory, the laboratory for routine safety analysis and genotyping , the CRO shall cooperate with the Sponsor to allow the fulfilment of such obligations;
c) strict compliance with the applicable data protection laws and this section of the protocol is deemed by the Sponsor as an essential condition of collaboration with the Site, the Principal investigator, the bioanalytical laboratory, the laboratory for routine safety analysis and genotyping, the CRO.

5.10.3 Data Controllers and Data Processors

The Sponsor and the CRO of which the Site is part shall act as independent data controllers for the personal data processing activities carried out within the Site's context. The CRO shall retain full decision making authority and responsibility regarding purposes and means of data processing operations related to treatment of Clinical Trial subjects at Site, including processing of medical records, registration of Clinical Trial subjects; Clinical Trial scheduling; Clinical Trial subjects recruitment; screening; Clinical Trial conduct and therefore shall act as independent data controller within the meaning of GDPR, even though the legal entity is not bound by GDPR; the CRO shall act and is hereby engaged as Sponsor's Data Processor for other personal data processing activities, performed by the CRO under the instructions of the Sponsor (such as data management activity, monitoring activity); the CRO has undertaken a Data Processing Agreement with the Sponsor .

5.10.4 Duties of the Parties involved in the Performance of the Study

Collection and use of subjects' personal data (i.e. subjects' data), including their biological samples, will be carried out in full respect of the provisions of the information notices submitted to subjects, as well as the privacy rights, the fundamental freedoms and the dignity of data subjects. All the parties involved in this study undertake to adopt adequate measures to warrant that data will always be processed securely and in compliance with privacy laws.
The Site, the Principal investigator, the Sponsor, the CRO as well as their appointed staff and service providers, each in its respective remit and within the limits of their specific role in the study, shall implement the following safety measures (physical, logical, organizational, technical, electronic, I.T. etc) to ensure adequate protection of the personal data of the subjects involved in the study. In particular:
(i) DATA SAFETY. The Site and/or the Principal Investigator shall adopt all the necessary measures to prevent or minimise the risks of theft, fire, flooding, partial or total loss, accidental disclosure or illegal/unauthorised access to study subject's data or Sponsor's proprietary confidential information; to this extent, before the beginning of the study, the Site and/or the Principal Investigator shall ensure that the actual measures they have implemented are fit-for-purpose and law-compliant, and in particular:
- in order to minimise the risk of unauthorized access and theft, the hardware on which subjects' personal data are stored shall be placed in a restricted-access area, accessible only

to those individuals who need to retrieve the subjects' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- any electronic database containing the subjects' personal data shall be placed in restricted-access area, accessible only to those individuals who need to retrieve the study subjects' personal data with usernames and password-protected by means of a strong password. Systems shall be set so that passwords must be updated at least every three months and feature at least 8 characters, with upper-case and lower-case recognition, containing "special" characters, such as upper case letters [A-Z], lower case letters [a-z], numbers [0-9], symbols [!, #, $, etc.] or other special characters [Á, ë, ö etc.]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her, such as name and year of birth (e.g. "johnbrown80") or easily predictable strings of characters (e.g. "qwerty", "12345", "admin", "user", etc.). If Site acts as Sponsor data processor based on mandatory local legislation/guidelines, the Site shall also implement multi-factor authentication in all databases where genetic data are processed;
- adequate cryptographic protection measures shall be put in place for data "at rest" and "in transit" (these include, for example, restricted user access, file system or database cryptography, or any other equivalent IT measure which renders data unintelligible or not accessible to those who are not authorised to access them);
- high level security measures shall be implemented also on the files or databases which contain the "key" to match the subjects' personal data (i.e. name, surname, etc.) with their respective "Study subject IDs" (as defined at point (iv) below);
- Backup processes and other measures that ensure rapid restoration of business-critical systems shall be implemented;
- Updated Antivirus and firewall programs shall be installed on the IT devices.

The Site shall regularly test and update the measures listed above.
The Site shall, upon request from the Sponsor, provide detailed written information about the measures listed above.
The CRO shall ensure the implementation of the above listed measures.
(ii) TRANSMISSION OF DATA. All the parties that transfer data through the internet and/or to the centralised database(s) used to process study's data or to generate statistical analyses shall implement secure protocols based on cryptographic standards which make data unintelligible to unauthorized individuals.
(iii) SECURITY OF THE CENTRALISED DATABASE. The centralised database held by the Sponsor shall have the following safeguards in place:
- appropriate authentication methods, which differentiate between different users according to their respective roles so as to ensure that access to a specific set of subjects' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study;
- appropriate measures to ensure that the authentication credentials are periodically updated (i.e. password change);

(iv) CODING (PSEUDONYMIZATION). All personal data that may allow identification of the subjects involved in the study shall be adequately dissociated from the other data pertaining to the study ("coding" or "pseudonymisation" process). The Principal investigator shall adequately dissociate the identification data of subjects from the data pertaining to the study by linking results to an alphanumeric code ["Subject ID"], whose format shall not make it possible to identify the study subject directly or indirectly, so as to ensure that only coded data are transmitted to the Sponsor and to the laboratories. Site/Principal Investigator shall

securely store a separate list (e.g.: identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above.
(v) SAMPLE STORAGE
As outlined below, samples shall only be stored for as long as strictly necessary for the study's performance until CSR finalization. Biological samples and any other examinations shall bear Subject ID, and in no case will they bear other information that may lead to the direct or indirect identification of the subject, especially when, in accordance with this protocol, samples shall be forwarded and shared outside the clinical Site (e.g. in case of centralized reading or local laboratory analysis).
(vi) TRAINING. The parties shall ensure that any personnel involved in the study have received proper training on data protection issues.
All actions related to the implementation of the aforementioned measures shall be provided by the Sponsor, and/or the Site/CRO to the competent authorities (including data protection authorities) and Ethics Committees if and when requested. If such authorities or the Sponsor consider the implementation of the aforementioned measures insufficient to guarantee an adequate level of protection of the subjects' personal data, the Site/CRO, the Principal investigator, and the laboratories undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

5.10.5 Archiving of the clinical trial master file and code pairing list

The Sponsor, the Site and the Principal Investigator will archive the content of the clinical trial master file, including the relevant subjects' personal data, for at least 10 years after the end of the clinical trial according to the Swiss laws (country where the study is performed). However, once the 10 years have expired, the parties will reassess any extension of the archiving up to 25 years or in accordance with current Swiss and European requirements. The study subject code pairing list (i.e. the list where the Subject ID is linked to the subjects' identification data such as name and surname), shall be archived by the Principal Investigator.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.
Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall undertake the responsibilities set out in this protocol.
The sponsor appoints the study manager or delegates as responsible person/s for archives. Access to archives shall be restricted to those individuals.

Once mandatory data retention time for the clinical trial master file has elapsed, the Site/Principal Investigator shall seek the authorisation of the Sponsor to destroy the clinical trial master file.

5.10.6 Data Breach

Data Breach is an incident regarding personal data security and leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed. In particular: destruction of personal data is where the data no longer exists, or no longer exists in a form that is of any use to the Site, Sponsor, CRO, Principal Investigator; data loss is when the data may still exist, but the Site, Sponsor, CRO, Principal Investigator has lost control or access to it, or no longer has it in its possession;

damage is where personal data has been altered, corrupted, or is no longer complete; data unavailability is where, following a data incident (such as a network outage, a natural or man-made disaster, etc.), personal data become temporarily inaccessible to the Site, Sponsor, CRO, Principal Investigator.

Anomalous Event is an event that is not part of the standard operational scope of an infrastructure, network or service and which affects, or is likely to affect, personal data; this may include theft or loss of IT devices and other physical events (e.g. an unauthorised access to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (e.g. cyber-attacks, default or hacking of cloud services), which may in any way entail loss, unavailability, alteration, theft, copy or dissemination of personal data.

Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach (see definitions above) affecting the subjects personal data and/or personal data collected in the context of the study, shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of an Anomalous Event and/or of a Data Breach) inform the Study Manager, the sponsor's Data Protection Officer, who may be contacted at dpo@menarini.com, the CRO (CROSS Research S.A.) and its responsible persons for data breach incidents management can be reached at privacy@croalliance.com and at the contacts shown at https://www.croalliance.com/privacy-policy respectively and shall provide the following information:

(i) Anomalous Event / Data Breach Type (e.g. data loss, unauthorized access, loss of company device, etc.);

(ii) Person or source that first reported the Anomalous Event/ Data Breach;

(iii) Date and Time when the person who first reported the Anomalous Event / Data Breach became aware of it;

(iv) Anomalous Event / Data Breach Date and Time (actual or presumed);

(v) Place (specify if actual or alleged) where the Anomalous Event / Data Breach occurred;

(vi) Anomalous Event / Data Breach Description;

(vii) Indicate the source of the Anomalous Event / Data Breach (e.g. I.P. source) - (if relevant);

(viii) Indicate the affected infrastructure / system / application / cloud/ software / hardware / database and their location;

(ix) List or describe the processing/storage systems affected by the Anomalous Event/Data Breach (if relevant);

(x) Number of data subjects involved (if known);

(xi) Amount of allegedly breached data

(xii) Other relevant information

Once all the above information has been provided, the Sponsor and/or the Site should have a reasonable degree of certainty that a security incident has occurred that has led to personal data being compromised.

Then, as appropriate, Sponsor and Site, each one in its respective remit, shall manage the Data Breach in accordance with the applicable data protection regulations.

For Data Breach affecting personal data of subjects of the European Union, Sponsor and Site autonomously or jointly - depending on the circumstances and their privacy responsibilities as defined by the Regulation 679/2016- shall:

1. Collect the necessary evidence and information;
2. Categorise the breach;
3. Determine the risk probability and level to the rights and freedom of the concerned subjects;
4. Identify and put in place appropriate remedies to minimise the impact of the Data Breach

5. Determine the notification and communication duties vis à vis the competent supervisory authority and/or the concerned subjects.

The requirements of the Swiss Federal Law on Data Protection (Law 235.1 of 19 June 1992 and subsequent updates) will be also fully satisfied.

5.10.7 Information notice on personal data protection and pseudonymisation

Prior to subjects' enrolment in the study, the Principal Investigator and/or the Site (including their personnel) shall provide each subject with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor and/or delegated CRO and shall collect his/her written consent to the processing of personal data according to the actual performance conditions in which the study is carried out. The Principal Investigator is responsible to archive the signed ICF in accordance with the security measures described above. Among other things, the ICF (or the separate form) shall inform subjects about:
(i) the applicable data protection legislation
(ii) the kind of data that shall be collected during the study listing them in detail or by category;
(iii) the purpose of data processing (for the performance of the study and / or for pharmacovigilance purposes and / or to register new medicines) and the legal basis;
(iv) whether granting the consent(s) to process personal data is a necessary or an optional condition to take part in the study (if the processing relies on consent as a legal basis);
(v) the use of data for future scientific research / secondary use of data (if any). In such a case the future scientific purposes / secondary use shall include studies for the registration of new medicines; studies which compare the data of this Study with other sources;
(vi) the coding (pseudonymisation) procedure and scope;
- (vii) who can access subjects' data and under what circumstances Principal Investigator and site for the study conduction, Sponsor for analysis of data, regulatory authorities for registration of new medicine and / or for inspections, the central lab for PK analysis. The complete list will be available upon request);

(viii) the period of data retention/storage as defined in [§ 5.10.5], including the storage of biological samples;
(ix) to which entities/countries outside Switzerland and the EU subjects' data will be transmitted e.g. USA. The complete list will be available upon request)
(x) subjects' data protection rights as defined by the EU General Data Protection Regulation 679/2016 and Swiss Federal Law on Data Protection (Law 235.1 of 19 June 1992 and subsequent updates).
(xi) Data Controllers / Data Processors and the relevant contact details
(xii) Sponsor's Data Protection Officer contacts (DPO)
(xiii) in case of genetic data processing the possible findings, also with regard to unexpected findings that might be disclosed on account of the processing of the genetic data.

5.10.8 Genetic Data

- The collection of genetic data for performing genetic tests and Screening shall be limited to the personal and family information that is absolutely indispensable for performing the study.

- If genetic data are processed in the context of the study for pregnancy follow-up purposes (pharmacovigilance) only (i) the collection of genetic data for performing genetic tests and Screening shall be limited to the personal and family information that is absolutely indispensable for pregnancy follow-up; (ii) the source, nature and mechanism for samples taking and storage will be under the pregnant health care provider and its local procedures; genetic data shall be processed pursuant to the applicable pharmacovigilance laws and regulations; genetic data shall be communicated/transmitted using high security standard. The provisions below shall be implemented as applicable from time to time.
- The source, nature and mechanisms for samples taking and storage will follow the appointed laboratory's procedures and will be described in the ICF.
- Without prejudice to applicable laws and regulations, except for data and results as per § 5.10, the protocol shall be subject to confidentiality obligations that will assure the secrecy of the data for at least one year after the conclusion of the study.
- The measures to keep subjects' identification data separated from biological materials and genetic information are reported in § 5.10.4 and § 5.10.5.
- Preservation, use, and transportation of biological samples shall be carried out in such a manner as to also ensure their quality, integrity, availability and traceability.
- Genetic data shall be transmitted electronically after encrypting or securing the communication of the information to be transmitted. Web application-based communication channels may be used if they rely on secure communication protocols.
- In order to minimise the risks of accidental disclosure and/or unlawful/unauthorised access, subjects' identities will be disclosed only when strictly necessary (e.g. to prevent a physical prejudice).
- Genetic and medical data will be processed (excluding the site) separately from any other personal data that can identify the subjects directly.
- The ICF and/or separate form will detail the possible findings regarding genetic data, also with regard to unexpected findings that might be disclosed as result of the test / elaboration of genetic data;
- The ICF and/or separate form will detail whether the data subject is allowed to limit the scope of communication of his/her genetic data and the transfer of biological samples, including their possible use for additional purposes;
- The ICF and/or separate form will detail the retention period of genetic data and biological samples (if different from the general retention period of other data processed in the context of the study).

5.10.9 Transfer of subjects' data outside Switzerland and the European Union

The study performance entails transferring subjects' personal data (coded data) outside Switzerland and the EU. To this extent, the Sponsor, the CRO/Site, the Principal investigator, the laboratories, undertake to export such data in compliance with adequate safeguards / legal basis as required by Swiss Federal Law on Data Protection (Law 235.1 of 19 June 1992 and subsequent updates) and the Regulation 679/2016 including the Commission Decisions, the Standard Contract Clauses, subjects' specific consent or, only where permitted under Chapter V of the GDPR, on one of the bases set out under art. 49 GDPR.
Examples of non-EU countries / entities are USA / Medidata. The complete list will be available upon request.

5.10.10 Exercise of subjects' data privacy rights

Each study subject has the right to contact the Sponsor, the CRO/Site, the Principal investigator, the laboratories, to exercise the rights afforded to the subject by the law, including those afforded by the Swiss Federal Law on Data Protection (Law 235.1 of 19 June 1992 and subsequent updates) and under articles 15 to 22 of Regulation (EU) 2016/679, namely: knowing whether or not any data referring to his/her is being processed in the context of the study; access his/her data; verify the data's content, origin, exactness, location (including, where applicable, the non-Swiss or EU countries where the data might be); obtain a copy of the data including their transmission to another entity indicated by the subject; ask that the data are supplemented, updated, amended; in the circumstances set forth by the law, ask that the processing of data is restricted, that data are anonymised or frozen; oppose to the processing of his/her data for legitimate reasons. Each subject has the right to lodge a complaint with his/her local supervisory authority and/or to notify to the Data Protection Officer any use of his/her personal data the subject regards as inappropriate.
Each study subject is free to withdraw at any time from the study. In such case, each study subject may ask the Sponsor, the CRO/Site, the Principal investigator, the laboratories, to destroy/delete his/her personal data (including his/her biological samples, unless they have been permanently anonymised), thus preventing any further processing or analysis of his/her data. However, data and results of tests that may have been used to determine the results of the study shall not be deleted, to avoid altering or impairing altogether the results of the study; study subjects will be properly informed of this before any study data is collected and they will have the possibility to refuse study participation.
Specific rights in relation to the processing of genetic data apply, please refer to § 5.10.8.
If the Site, the Principal investigator, the Centralised Laboratory, the CRO receive a request for data privacy rights exercise, the concerned recipient shall immediately inform the Sponsor DPO by email at dpo@menarini.com.
The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the CRO/Site, the Principal investigator, the laboratories shall implement adequate organisational measures to reply to subjects within the above-mentioned deadline.

5.10.11 Future research

With subjects' optional and additional consent, the Sponsor and / or the site may use the data collected during the course of the study for further medical and scientific research purposes. These may include, for example: retrospective clinical studies; studies which compare the data of this study with those from other sources to identify the factors involved in a disease; registration of new drugs. In the context of these additional research activities, subjects' data will be processed, coded (pseudonymised) and transferred abroad and may be shared with future research partners.

6 STUDY RATIONALE AND BACKGROUND INFORMATION

6.1 Investigational medicinal product

The treatment with fixed combinations for cardiovascular chronic diseases is common as they are expected to improve therapeutic compliance over the same drugs administered separately,

as outlined in the EMA guideline on clinical investigation of medicinal products in the treatment of hypertension. [3]
Menarini Ricerche is developing a film coated oral tablet where Nebivolol and Ramipril are formulated in fixed dose combination to support the indication of substitution therapy in hypertensive patients whose blood pressure is adequately controlled on Nebivolol and Ramipril given concurrently. In order to cover the doses in consolidated use for the treatment of hypertension, three different fixed combination (FDC) strengths are being developed including Nebivol 5 mg with Ramipril 2.5 mg, 5 mg and 10 mg.
Based on the pharmaceutical and pharmacokinetic characteristics of the two drugs, in accordance to the EMA guidelines CPMP/EWP/QWP/1401/98 Rev. 1, including its Biopharmaceutics Classification System (BCS)-based biowaiver appendix, the indication for substitution therapy of all 3 different strengths can be supported by the demonstration of the bioequivalence at the highest dose strength of the two drugs (namely Nebivolol 5mg and Ramipril 10 mg) formulated as FDC versus their extemporaneous co-administration.

Based on this rationale, the proposed study aims to demonstrate the bioequivalence of the FDC of Nebivolol 5 mg and Ramipril 10 mg (hereinafter reported as NEB/RAM 5/10 mg) administered as one oral film-coated tablet and representing the Test Formulation versus the Reference Formulation represented by extemporaneous co-administration of the EU authorised products Nebivolol 5 mg tablet plus Ramipril 10 mg tablet (hereinafter reported as NEB+RAM 5 mg+10 mg EC).

Nebivolol is a potent and selective ß1-adrenergic antagonist that also exhibits nitric oxide (NO)-mediated vasodilatory effects. It is a 50:50 racemic mixture of the enantiomeric pair (+)-Nebivolol and (-)-Nebivolol. The drug is devoid of intrinsic sympathomimetic activity.
Nebivolol metabolism involves the CYP2D6 isoenzyme. Following its oral administration in humans, peak plasma concentrations are reached around 1-hour post-dosing. In extensive CYP2D6 metabolizers, the drug is characterized by an elimination half-life of around 10-12 hours, this value being longer (up to 3-5 times) in poor metabolizers. [4], [5]
Nebivolol was first registered in The Netherlands in October 1995 for the treatment of hypertension and is now registered in many European and Extra-European countries.
Nebivolol is available on the market as tablets containing 5 mg of active substance (Nebilet®) and is currently indicated at the dose of one tablet 5 mg/day in the treatment of essential hypertension as well as stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients ≥ 70 years. Main product characteristics of Nebivolol are summarised in the reference SmPC of Nebilet® 5 mg [6].

Ramipril is the prodrug of the active metabolite ramiprilat, a potent and long-acting inhibitor of the angiotensin-converting enzyme (ACE). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilation.
Following oral administration, ramipril is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite ramiprilat after oral administration is 45 %. Peak plasma concentrations of ramiprilat, the sole active metabolite of ramipril, are reached 2-4 hours after ramipril intake. Steady state plasma concentrations of

ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.
Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy is lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.
Ramipril has been authorised in the EU since 1989, first in France and then in many other European and Extra-European countries. Ramipril is available on the market as tablets of 1.25 mg, 2.5 mg, 5 mg and 10 mg strengths and is currently indicated for the treatment of essential hypertension as well as treatment of symptomatic heart failure and renal disease (glomerular diabetic and non-diabetic nephropathy).

Main product information is summarised in the Summary of Product Characteristics (SmPC) of Cardace® (10 mg) [7].

6.1.1 Non-clinical data

Nebivolol and Ramipril as single agents underwent extensive non-clinical programs.
For non-clinical information reference is made to the approved Nebilet® 5 mg and Cardace® (10 mg) SmPCs [6,7].

6.1.2 Clinical experience

Nebivolol and Ramipril have been in the market for about three decades.

Nebivolol has been evaluated for the treatment of hypertension, both as monotherapy and in combination with other classes of antihypertensive agents. The approval of Nebivolol for the treatment of hypertension was based upon evidence of its efficacy and safety in three large, randomized, placebo-controlled 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 [4, 5].

Large-scale double-blind multicentre studies have demonstrated that the antihypertensive efficacy of Ramipril is comparable to that of enalapril, captopril, lisinopril and atenolol. In placebo-controlled studies, once daily administration of Ramipril 2.5 to 20mg 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 [8].

6.2 Risk Benefit Assessment

The planned NEB-RAM-01 study aims to demonstrate in healthy subjects the bioequivalence of the FDC versus already marketed mono components in extemporaneous combinations, as they are commonly used in the ordinary clinical setting to treat hypertensive patients. No direct benefit is expected for the subjects who take part in the study.

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 subjects aged between 18 – 60 years old who have successfully passed the Screening evaluating their well-being status based on anamnesis, physical examination, clinical and laboratory parameters.

Significant hypotensive effect is not expected following the administration of single dose of Nebivolol 5 mg and Ramipril 10mg; however, as mitigation action subjects 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 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 ($t_{1/2}$ of 12 h considered for Nebivolol). Genotyping of eligible participants also excludes poor and intermediate CYP2D6 metabolizers, thus minimising 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 [6,7] prior to leaving the Unit. Monitoring of cardiovascular parameters (blood pressure, pulse rate and ECG) are also included at different time points post-treatment administration 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 in repeated blood sampling for PK analysis. The total blood volume which will be withdrawn for PK and laboratory safety tests is standard and acceptable, taking the study population (healthy subjects) 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 occurrence of clinically significant findings.

6.3 Risk benefit assessment for COVID-19 pandemic

Both, EMA and FDA, as well as national health authorities in Europe have issued guidelines that aim to provide recommendations for actions to conduct clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may change at a high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect subjects participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the EMA guideline.
Nebivolol and Ramipril are not expected to interact with the immune system. Both are not known to inhibit innate or adaptive immunity.
Nebivolol is a potent and selective ß1-adrenergic antagonist that also exhibits nitric oxide (NO)-mediated vasodilatory effects. No negative effects of the ß1-adrenergic antagonist class

(including Nebivolol) in the course of an infection with SARS-CoV-2 are reported in the recent scientific literature.
Ramiprilat, the active metabolite of the prodrug Ramipril, inhibits the ACE. In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilation. On the basis of preclinical models in rats, it was postulated that ACE inhibitors might lead to an upregulation of angiotensin-converting enzyme 2 (ACE2), a membrane-bound enzyme located in several organs including the lung. ACE2 is assumed to function as a receptor for SARS-CoV-2. However, current data do not suggest a higher risk for SARS-CoV-2 infections or a poor Coronavirus disease 2019 (COVID-19) disease prognosis due to the use of ACE inhibitors.

In the bioequivalence study NEB-RAM-01, Nebivolol and Ramipril are administered as single doses (5mg and 10mg, respectively) of a fixed or extemporaneous combination.
Although the target of the primary pharmacodynamics is the cardiovascular system, and some undesirable pulmonary/cardiovascular effects in humans are known, it is unlikely that single doses of Nebivolol and Ramipril have substantial effects on the cardiopulmonary system that affect the course of COVID-19 disease in case the subject acquires SARS-CoV-2.
Therefore, the risk of the subjects to develop COVID-19 is expected to be similar to the general population. However, the risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (e.g., commute to the site) and have additional human contact (e.g., with site staff and other participants of the clinical study).
Measures implemented to mitigate the additional risks caused by COVID-19 are:

- This study is going to start enrolment only when the Sponsor in collaboration with the CRO deem it is safe to start the study.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.

Subjects will be tested for COVID-19 within the 48 h prior to any admission to the Clinical Unit.

7 STUDY OBJECTIVES

7.1 Primary Objective

The primary objective is to evaluate the bioequivalence of the NEB/RAM 5/10 mg FDC (Test) versus NEB 5 mg + RAM 10 mg EC (Reference).

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan Description

This will be an open label, randomized, two treatment, three period, three sequence, single dose partial replicate cross-over study to assess the bioequivalence of the Nebivolol/Ramipril 5/10 mg FDC (Test) versus Nebivolol 5 mg and Ramipril 10 mg administered as extemporaneous combination (Reference).

The study population will include 54 healthy males and females (18 subjects per each randomized sequence), aged 18 to 60 years inclusive, who successfully pass the Screening procedures and will receive single doses of Test and Reference formulations according to the assigned randomized sequence A, B or C, as described in the schematic study design, § 2.1.

Subjects will undergo a Screening (to be performed within overall 4 weeks prior to 1st study PK session), three PK sessions with one single dose administration of the Test Formulation in one out of the 3 PK sessions and one single dose of the Reference Formulation in two of the 3 PK sessions as per sequence assigned by randomization. Each PK session is separated by a minimum of a 14-day period between each IMP intake. In each PK session, blood sampling for PK plasma assessment will be taken at predefined time points up to 72 hours (h) post-dose. An End of Study Visit will be performed 10-12 days after last treatment administration, resulting in an expected individual overall clinical study duration of about 10 weeks.

In case of any serious adverse (drug) reaction (SAR), subject enrolment and treatment administration will be put on-hold or stopped. The study will be resumed only after the case has been discussed and a decision on how to proceed has been taken by the Sponsor.

8.2 Discussion of study design, including the choice of control group

The study is designed according to the recommendation provided by the current international guidelines on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1).
The three-period, three-sequences, cross-over design with the replicate PK for the Reference formulation has been selected to allow the evaluation of the Reference intrasubject variability that has been reported for Ramipril to be > 30%. If confirmed in this study, the criteria for declaring the bioequivalence might be adjusted as contemplated by the above-mentioned guidelines.

Treatment administration will be separated by a wash-out period of at least 14 days that is sufficient to ensure that plasmatic drugs concentrations of Ramipril and Ramiprilat and also nebivolol (being poor and intermediate metabolizers not eligible to the study) are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second/third PK study session. For Ramipril and Nebivolol a wash-out period of at least 14 days (> 5 half-lives) between each IMP intake is estimated to be adequate to reach a complete plasmatic clearance.

Each randomised subject will be allocated to a sequence of treatment administrations in the three study periods (A, B or C) according to a computer-generated randomisation list.

An open-label design was selected since the primary objective of the study is based on objective measurements of the analytes in plasma and the outcome variables could not be influenced by the subjects or Investigator being aware of the administered products.

The rationale for dose selection is presented in § 6.1.

The mitigation procedures implemented at screening and over the study conduct in order to reduce the risk of COVID-19 infection are deemed appropriate for its conduct in healthy subjects under the evolving COVID-19 pandemic (see § 6.3).

8.3 Selection of Study Population

After providing informed consent, the eligibility of the subjects to enter this study will be assessed based on the inclusion and exclusion criteria which will be checked at Screening and rechecked prior to the dosing procedure during the 1st, 2nd, and 3rd PK session.
Subjects will be included into the study only if they meet all the inclusion criteria (see § 8.3.1), they do not meet any of the exclusion criteria (see § 8.3.2) and if they agree to accept the restrictions that come with participating in this study (see § 8.3.3).

8.3.1 Inclusion criteria

To be eligible for this study, EACH of the following criteria must be satisfied:

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 must be using 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 agrees to use a male condom with spermicide
    - A sterile sexual partner
    - 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 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.

8.3.2 Exclusion criteria

To be eligible for this study, NONE of the following criteria must be satisfied:

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 (10)], 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 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. 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 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, food supplement in the last 14 days prior to the dosing.
17. Subjects 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 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, 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 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 has 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.

8.3.3 Screening Failures

Screening failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomly assigned to the study product or entered in the study because they do not meet one or more criteria required for participation in the trial.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Rescreened subjects should be assigned to a different subject number with respect to the one assigned on the initial Screening.

8.3.4 Study restrictions (when applicable)

Subjects will be asked to adhere to the following study restrictions along their study participation, which are also listed and explained in the ICF.

- Subjects are requested not to do strenuous physical exercise from 48 h prior to the clinical assessment at Screening and from 48 h prior to the admission to the study site for the first PK session until completion of the End of Study Visit.
- Subjects will be required to fast for at least 10 hours overnight prior to the morning dose in each of the PK study sessions. The fast will be broken approximately 4 h after dosing with a light standard lunch.
- From 48 h prior to dosing and until the last PK sample is collected during each PK study session, subjects are requested to avoid any food and drinks rich in caffeine or xanthine (e.g., chocolate, coffee, tea, cola beverages). The subjects should also not take any disallowed substances/concomitant medications/herbal remedies/food supplements,

according to time defined in § 8.3.1, 8.3.2 and 9.3.4.
- The subjects also have to avoid food containing poppy-seeds for 3 days before the test for drug of abuse is performed at each admission to the clinical unit (see study flow chart on §2.2), as this can lead to a positive result.
- Alcohol consumption is not allowed from 48 h prior to the clinical assessment at Screening and from 48 h prior to admission to the study site for the first PK session until completion of the End of Study Visit.
- COVID-19: Subjects are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory.

On each PK study session, after dosing, the subjects will remain sitting or in a semi-recumbent position for the first 4 hours. Subjects will not be allowed to drink any water 1 hour before and 1 hour after the dosing, with the exception of water foreseen for treatment administration. In order to maintain adequate hydration, the subjects will be encouraged to drink at least 180 mL of still mineral water every 2 h for 5 h post-dose, starting at 1 h post-dose.

Standardised meals will be served at predefined time points, with lunch at approximately 4 hours after each dosing.
In case of overlap, study procedures will be completed before food intake.

8.3.5 Withdrawal of subjects from treatment or assessment

Participation in the study is strictly voluntary and subjects have the right to withdraw from the study at any time without explanation. Subjects may also be withdrawn at the Investigator's discretion or at specific Sponsor's request at any time.
In the event that the subject withdraws from the study for whatever reason, the Investigator must be informed immediately and the date, reasons, and circumstances for premature discontinuation will be documented in the corresponding section of the (e)CRF. Subjects have to discontinue the study if they experience:
- Adverse Event, including clinically significant abnormal laboratory value(s) which request study termination according to the Investigator's judgement.
- Symptomatic hypotension with at least moderate symptoms.
- Protocol Violation (e.g., prohibited medication, poor compliance with study procedures / treatment).
- Subject's request.
- Pregnancy.

In case a subject becomes positive for SARS-CoV-2 infection after being randomized, a 2-week window will be allowed for recovery. By the end of this period, if the subject recovers from the infection (i.e. negative test at the admission to the site), he/she may resume the study participation if the investigator deems it appropriate. Otherwise the subject will be withdrawn from the study and considered as a drop out. Subjects may be discontinued from the study at the discretion of the investigator to protect their safety or the safety of other participants.

Any subject who prematurely terminates participation and who has received the study medication will be encouraged to undergo the End of Study Visit.

If study participation is terminated due to an AE, the subject has to be followed-up by additional examinations according to the medical judgement of the Investigator, until the abnormal condition is resolved or the Investigator deems further observations or examinations are no longer medically indicated.
If a subject prematurely terminates the study, data already collected will be used and analysed for the purpose of the study.
In regard to biological samples already collected, the subject that has withdrawn the consent can require that his/her samples already obtained but not yet analysed are destroyed.

9 INVESTIGATIONAL PRODUCT(S)

9.1 Identity

Nebivolol HCl

INN:	Nebivolol HCl
Chemical Name:	[2R*[R*[R*(S*)]]]-α,α'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride
Dose:	5 mg (Nebivolol)
Dosage form:	Tablet
Route of administration:	Oral administration

Ramipril

INN:	Ramipril
Chemical Name:	(2S,3aS,6aS)-1-[(2S)-2-[[(2S)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid
Doses:	10 mg
Dosage form:	Tablet
Route of administration:	Oral administration

9.2 Description of Investigational Medicinal Product(s)

The Test formulation of NEB/RAM 5/10 mg is a film-coated tablet for oral administration.
One film-coated tablet contains 5 mg Nebivolol (corresponding to 5.45 mg of nebivolol hydrochloride) and 10 mg Ramipril, as well as the following inactive ingredients: microcrystalline cellulose, native maize starch, croscarmellose sodium, hypromellose, polysorbate 80, sodium stearyl fumarate, and OPADRY® Y-1-7000 white. The OPADRY® ingredient complies with the respective manufacturer's specification.

The Reference medication consists of one film-coated tablet nebivolol 5 mg (corresponding to 5.45 mg nebivolol hydrochloride) and one tablet Ramipril 10 mg.
Authorized EU market preparation of Nebivolol 5 mg tablet (Nebilet®) and Ramipril 10 mg tablet (Cardace®) will be used as reference drug products.

9.2.1 Packaging, labelling, and storage

Packaging: Primary packaging of NEB/RAM 5/10 mg film-coated tablet is performed under the responsibility of Saneca Pharmaceuticals a.s., Nitrianska 100, 920 27 Hlohovec, Slovak Republic. The Test formulations will be packaged in blisters (primary packaging).
The Reference medication consists of authorised EU market preparations, Nebivolol 5 mg tablet (Nebilet®), Ramipril 10 mg tablet (Cardace®).
The secondary packaging and labelling of both Test and Reference medication as IMP are performed under the responsibility of the Department of Pharmaceutical Development of A. MRBS, Glienicker Weg 125, 12489 Berlin, Germany.
The blistered tablets are permanently fixed in blister cards (secondary packaging) according to the study design.
Distribution of IMP boxes will be under the responsibility of A. MRBS.
Labelling: The IMP will be labelled in compliance with the current valid international and corresponding national requirements.
Storage: At the study site, the IMP must be kept in a secure area inaccessible to unauthorised individuals and stored at a temperature that does not exceed 25°C, according to the storage conditions given on the label.

9.2.2 Drug accountability

The Investigator and / or a designee appointed by him / her will maintain records of the product delivery to the trial site, the inventory at the site, the use by each subject and the return to the Sponsor or any alternative disposition of used / unused product.
Upon receipt of all study medication, the recipient (study site personnel) will open the shipment package and verify the contents as stated in the enclosed Delivery Note. Every receiving party (study site) has to immediately fill in and sign the enclosed form "Handing over and delivery receipt of CTM". The final recipient, i.e., the study site personnel should keep a copy and send the form via Fax or e-mail to A. MRBS to confirm the receipt of the study medication.
The Investigator or designee will be responsible for maintaining the dispensing records detailing the allocation of medication to subjects. The study drug administration will be documented also in the eCRF.

9.2.3 Destruction of surplus medication

At the end of the study, all remaining IMP will be reconciled under the responsibility of the Investigator at the site, collected and returned to A. MRBS for destruction, provided that this is not in conflict with any national export legislation, or destroyed on site (upon written authorisation). If applicable, IMP returns will be organized by A. MRBS. In case the IMP is destroyed locally, the certificates of destruction should be provided to the Sponsor.

9.3 Treatments

9.3.1 Treatment administration - frequency and duration of application

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). Sequence of treatments (Table 1) will follow the randomization list.
The test and the reference formulation will be taken as single doses in fasting condition on three separate study sessions (a minimum of 14-day wash-out period between each IMP intake is requested), swallowed by the subjects in a sitting or upright position with a total volume of 240 mL of still water. Study drugs will be dispensed only under the restricted conditions defined in the present protocol at the study site and will be administered by the Investigator or under his/her direct supervision.
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. The actual time of administration of each tablet will be recorded on the medical records and eCRF. The time of first tablet intake is considered as the dosing time for post administration assessments.

9.3.2 Randomisation and blinding

The study will be performed according to an open design with treatment sequence allocated to each subject according to the randomisation list; no blinding technique will be used.
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.
The scheme of treatment sequences A, B, C is displayed in Table 1.

Table 1. Treatment sequences

	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

9.3.3 Treatment compliance

Study treatment will be administered at the site, under the direct supervision of the Investigator or delegate. The study drug administration will be documented also in the eCRF.

9.3.4 Prior and Concomitant Medication

It will not be permitted to take ANY other medications within 21 days or 5 half- lives of the product, whichever is longer, prior to dosing and during the study conduct, in particular:

- paroxetine, fluoxetine, thioridazine, quinidine, cimetidine, nicardipine and antacids
- lithium, potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), sodium
- aurothiomalate,
- tricyclic antidepressants, antipsychotics, barbiturates,
- cyclosporin, tacrolimus, allopurinol, procainamide, sildenafil, simvastatin.

The only exception is short-term paracetamol use up to 1.5 g/day (ONLY if required as per Investigator's judgement) and oral contraceptives (see later in the text).
Moreover, herbal remedies and food supplement consumption will not be allowed within 14 days prior to dosing and during the study conduct.
Oral contraceptives, injectable contraceptives, contraceptive implants will be allowed if the subject has been taking them for at least 1 month prior to Screening Visit.
If the administration of a prohibited medication becomes necessary during the clinical study, then the Sponsor must be consulted. A decision will then be taken as to whether this subject should discontinue the study. All medications taken since the inclusion in the study until the End of Study Visit will be recorded in the Prior and Concomitant Medications section of the eCRF. The details to be reported in eCRF are: type of medication, indication, dose, route of administration and duration.

9.4 Study Procedures and Assessments

The study encompasses the Screening, three PK study sessions and the End of Study (EOS) Visit. EOS visit should be performed, as far as possible and with the subject's consent, in case of the early discontinuation from the study.

As part of the COVID-19 risk mitigation, RT-PCR or a rapid antigen test will be performed in the 48 hours prior subjects' Phase I Unit residence (i.e. day before first dosing day).
In case a subject is positive for SARS-CoV-2 infection after being randomized, a 2-week window will be allowed for recovery. By the end of this period, if the subject recovers from the infection (i.e. negative test at the admission to the site), he/she may resume the study participation if the investigator deems it appropriate, otherwise the subject will withdraw from the study and be considered as drop out.

9.4.1 Study Procedures

9.4.1.1 Informed consent process

Eligible subjects can only be included in the study after they have provided the written informed consent. Study procedures will be explained to the subjects and their written informed consent must be obtained before starting any procedure required by the protocol. All subjects will be also informed on the required restrictions detailed in § 8.3.4.

The process of obtaining the informed consent shall be documented in the subject source documents.

9.4.1.2 Screening *(within 4 weeks prior to 1st PK study session, including genotyping)*

At Screening, each subject will attend the study site in fasting condition (for at least 10 h) for the following procedures:

- Collection of demographic data.
- Recording of medical history, including prior and concomitant medications.
- Physical examination, including height and weight to calculate BMI.
- Recording of vital signs including Frontal Body Temperature, supine, and SBP, DBP, PR, RR and 12-lead ECG, to be measured after at least 10-minute rest. In addition, SBP and DBP are to be measured after standing for 2-5 minutes.
- Blood sampling for:
  - Genotyping for CYP2D6 mutational status (see § 9.4.2)
  - Haematology and biochemistry safety laboratory tests.
  - Serology for HIV I and II, HBV and HCV.
  - Pregnancy test (β-HCG in serum) in female subjects (if applicable)
- Urine collection for:
  - Drugs of abuse 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);
  - Cotinine;
  - Urinalysis.
- Alcohol salivary test.
- Recording of any Clinical Event, not associated to any drug intake (Clinical Event; § 9.5.2.3) and/or of any Adverse Event (§ 9.5.3.1), associated to any drug intake that occurs for the first time or worsens after the signature of the Informed Consent and prior to Investigational Medicinal Product (IMP) administration, if any.
- Check of inclusion/exclusion criteria.

Subjects who do not meet ALL inclusion criteria or meet ANY of the exclusion criteria listed in § 8.3.2 and § 8.3.3, respectively, and those with any clinically significant abnormality (including laboratory values, vital signs and 12-lead ECG) will not be considered as eligible to be randomized to study treatments and will not continue the study.

Once a subject's eligibility has been confirmed, the dates for the three PK study sessions shall be scheduled and the subject shall be instructed to attend the study site in the evening of the day prior to each PK study session and to adhere to the study restrictions as reported in § 8.3.4.

NOTE 1: re-screening to evaluate subject's eligibility is allowed provided that the subject has not already been randomized.

NOTE 2: Genetic evaluation of CYP2D6 activity is not required if previous results are made available to the Investigator.

9.4.1.3 Pharmacokinetic Study Sessions

Subjects will be resident at the study site from the evening of the day prior to each PK study session until the 72-h post dosing, after PK sampling and study procedures have been completed.
Each study session should be separated by a minimum of 14-day wash-out period between each IMP intake.
Subjects must abstain from extraneous exercise during residence at the study site.
Study procedures to be applied to the PK study sessions are described below.

Pre-dosing procedures will be performed as follows:
NOTE: pre-dosing procedures can be performed on Day - 1, i.e. the day before dosing, the only exception being the 'Baseline' procedures listed below)

- Recording of any Clinical Event, not associated to any drug intake (Clinical Event; § 9.5.2.3 NOTE) and/or of any Adverse Event (§ 9.5.2.3), associated to any drug intake that occurs for the first time or worsens after the signature of the Informed Consent and prior to IMP administration, if any, and/or any medication change since the screening visit/previous study session, if any.
- Check of adherence to the study restrictions.
- Physical examination.
- Urine collection for:
  - Pregnancy test (β-HCG in urine) in female of childbearing potential.
  - Drugs of abuse 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).
  - Cotinine test.
- Alcohol salivary test.
- Re-check of inclusion/exclusion criteria.
- Randomization (applicable to 1st PK session only).
- Baseline recording (T+0'), within 1 hour from dosing of vital signs including Frontal Body Temperature, supine SBP and DBP, PR, RR and 12-lead ECG, to be measured after at least 10-minute rest.
- Baseline blood sample (T+0') of 8 mL for PK plasma assay within 30 minutes from dosing.

Dosing will start after baseline (prior to dosing) procedures are completed, with one of two oral treatments to be administered as per randomization sequence:

- NEB/RAM 5/10 mg FDC;
- NEB 5 mg + RAM 10 mg EC;

All treatments shall be orally taken in the morning, at 8:00 ± 1 h, in fasting condition with 240 mL of still water.

NOTE: The two tablets of the extemporaneous combination should be taken almost simultaneously, i.e. one immediately after the other, with Nebivolol to be taken first, followed by Ramipril tablet. Intake time will be recorded for each tablet.

Subjects will be required to fast for at least 10 h overnight prior to each morning dose. The fast will be broken approximately 4 h after dosing with a light standard lunch. Subjects will not be allowed to drink any water 1 h before and 1 h after the dosing, with the exception of water foreseen for treatment administration.
In order to maintain adequate hydration, the subjects will be encouraged to drink at least 180 mL of still mineral water every 2 h for 5 h post-dose, starting at 1 h post-dose.

After dosing, the following procedures will be performed:

- Recording at T+1.5 h, T+6 h, T+ 12h and T+ 24h of vital signs including supine SBP and DBP, PR, and 12-lead ECG, to be measured after at least 10-minute rest (when overlapping, recording to be done within 30 min before PK sampling)

Blood sampling for PK analysis (8 mL: 5 mL for Nebivolol and 3 mL for Ramipril and Ramiprilat, each), for plasma assay at the following predefined time points:

Nebivolol and Ramiprilat PK samples: T+5', T+15', T+30', T+45', T+1h, T+1.25h, T+1.5h, T+2h, T+2.5h, T+3h; T+3.5h, T+4h, T+6h, T+8h, T+10h, T+12h, T+24h, T+48h and T+72h post dose.

Ramipril PK samples: T+5', T+15', T+30', T+45', T+1h, T+1.25h, T+1.5h, T+2h, T+2.5h, T+3h; T+3.5h, T+4h, T+6h, T+8h, T+10h, T+12h, T+24h, post dose.

A time window for blood sample collection is allowed as follows:
± 2 minutes for blood sampling from T+15' to T+4h;
± 5 minutes for blood sampling from T+5h to T+24h;
± 30 minutes for blood sampling from T+48h to T+72h.

Before discharge from the Unit,
Recording of any AE that occurred during all the experimental phase and of all the concomitant medications taken, if any.

9.4.1.4 End of Study Visit (10-12 days after last treatment administration)

The following examinations and tests will be performed during this visit:

- Recording of vital signs including Frontal Body Temperature and supine SBP and DBP, PR, RR and 12-lead ECG, to be measured after at least 10-minute rest.
- Physical examination
- Blood sampling for haematology and biochemistry.
- Urine collection for:
  - Pregnancy test (β-HCG in urine) in female subjects (if applicable),
  - Urinalysis.
- Recording of AEs that occurred between the last study session and the End of Study visit and concomitant medications taken, if any.

The total amount of blood that will be collected for safety and PK assessment during the whole study duration is approximately 506 mL (see Table 2).

This volume only slightly exceeds a normal blood donation and is collected in a time period of at least 2 months.

Table 2. Total blood volume withdrawn relative to Screening, 3 PK sessions and End of Study Visit.

Sample type	**Volume (mL)**	**Number**	**Sub-Total (mL)**
PK	8	60	480
Biochemistry	8.5	2	17
Haematology	4	2	8
HIV-1, HIV-2, HBV, HCV*	NA	NA	NA
CYP2D6	1	1	1
			TOTAL=506 mL

*Volume included with Haematology volume (also Volume for pregnancy test in serum at screening is included)

9.4.2 Sample collection for CYP2D6 analysis

In order to only include normal metabolizers for CYP2D6 based on the genotype, subjects will be assessed for their CYP2D6 mutational status. A blood sample collected during Screening will be used for this assessment. CYP2D6 will be analysed using next-generation sequencing (NGS). Each genetic testing result will include information on the identified genetic variants as well as metabolizer classification (poor, intermediate, extensive or ultra- rapid metabolizers) and clinical interpretation of the result.

9.4.3 Assessment of Pharmacokinetics

9.4.3.1 Calculation of pharmacokinetic parameters

Pharmacokinetic parameters for Nebivolol, Ramipril and Ramiprilat will be derived from individual measured concentrations by means of non-compartmental analysis (NCA) using Phoenix™ WinNonlin® software, version 8.3.5 or higher (Pharsight Corp., Mountain View, California).

The following PK parameters will be determined following partial replicated administration of Test and Reference formulations, as appropriate, by period, resulting in 2 PK profiles for EC, and one PK profile for FDC.

C_{max}	Maximum plasma concentration
t_{max}	Time to C_{max}
C_{last}	Last quantifiable plasma concentration observed
t_{last}	Time corresponding to C_{last}
λ_z	Apparent terminal elimination rate constant, estimated by log-linear regression analysis on plasma concentrations visually assessed to be on the terminal log-linear phase.
$t_{1/2}$	Plasma terminal half-life, calculated according to the following equation: $t_{1/2} = \frac{0.693}{\lambda_z}$
$AUC_{(0\text{-}t)}$	Area under the plasma concentration-time curve from time zero (baseline) to the time of the last quantifiable concentration, calculated by means of the linear-log trapezoidal method
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from time zero to infinity, calculated according to the following equation: $AUC_{(0\text{-}\infty)} = AUC_{(0-t)} + \frac{C_{last}}{\lambda_z}$
$AUC_{(0\text{-}72)}$	Area under the plasma concentration-time curve from time zero (baseline) to 72h post-dose
$\%AUC_{extrap}$	The percentage of AUC $(0-\infty)$ obtained by extrapolation ($\%AUC_{extrap}$) will be calculated as follows: $\%AUC_{ex} = \frac{AUC_{(0\text{-}\infty)} - AUC_{(0\text{-}t)}}{AUC_{(0\text{-}\infty)}} \times 100$

Other PK parameters can be calculated, if considered appropriate and justified at the time of the PK analysis.

Actual PK sampling times will be used in the derivation of non-compartmental PK parameters. Nominal sampling times may be used as a replacement for unknown or missing actual times.

Concentration values below the Lower Limit of Quantification (LLOQ) will be set to zero. Concentrations reported as >LLOQ at time zero, when the subject has not previously been dosed, will be set to their real value.

Individual concentrations deemed to be anomalous will not be excluded from the PK analysis and mean profiles; anyway, such anomalous values will be identified in the relevant tables of study report. Anomalous values are those that are inconsistent with known or expected PK behaviour of the drug, and are not defined in a statistical outlier sense. Exclusion of data can be accepted only under the following circumstances:

- Drop out/withdrawn subjects
- A subject with lack of any measurable concentrations or only very low plasma concentrations for reference formulation. A subject is considered to have very low plasma concentrations if its AUC is less than 5% of reference medicinal product

geometric mean (GM) AUC (which should be calculated without inclusion of data from the outlying subject).

- Subjects with non-zero baseline concentrations > 5% of C_{max}. Such data will be excluded from bioequivalence calculation. The above can be due to subjects' noncompliance and/or to an insufficient wash-out period.
- A subject may be excluded from the PK population if there are any important protocol deviations or adverse events (AEs) that may impact PK. Additional details on exclusion criteria will be provided in the SAP.

Clear justification will be provided in the report for exclusion of any data.

9.4.2.2 Sampling and handling of pharmacokinetic blood samples

Blood samples for PK plasma assay of Nebivolol, Ramipril and Ramiprilat analytes (8 mL: 5 mL for nebivolol and 3 mL for Ramipril and Ramiprilat, at each time-point) are required from T+0 (baseline) up to 72 h post dose as reported under § 9.4.1.2.

Actual sampling times for each subject will be recorded in the individual electronic case report forms (eCRFs). The actual sampling times should not exceed the recommended tolerance ranges presented in the section above. Any deviation outside the recommended ranges will be verified through automatic queries and, if confirmed, will be reported as protocol deviation, although it will not automatically lead to the exclusion of the concerned subjects from the PK population.
The total amount of blood collected from each subject for PK assessment for the overall study sessions is up to 480 mL.

Blood samples for PK analysis will be collected using an indwelling catheter with switch valve. The cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution. The first 1 mL of blood will be discarded at each collection time from the cannula.

The remaining blood volume will be collected from the catheter and transferred with a syringe into heparinised tubes (Li-heparin).

The samples will be stored on ice for a maximum of 30 min. Then they were centrifuged at 4° C for 10 min at 1900 g to obtain plasma. Each plasma sample was immediately divided into 4 aliquots in pre-labelled polypropylene tubes:

- P1 and P2 (for Nebivolol) with 0.8 mL each
- P3 and P4 (for Ramipril and Ramiprilat) with 0.5 mL each

If the plasma obtained is insufficient, transfer the required volume in aliquots P1 and P3 and the remaining volume in aliquots P2 and P4.

All the aliquots were stored frozen, at temperatures -80ºC (±15ºC), within 30 min from the end of centrifugation.

9.4.2.3 Samples labelling

Each sample tube will be clearly and unequivocally identified with a label resistant to the storage temperature and reporting:

Study code	Study CRO-PK-23-364 - Sponsor code NEB-RAM-01
Subject number	
Tube identification	P1/P2/P3/P4
Period	
Study day	
Scheduled sampling time	as h

9.4.2.4 Samples storage and transport

During the study the samples will be stored at -80ºC (±15ºC). At the end of each collection day, P1/P3 and P2/P4 aliquots will be stored in separate freezers.

All P1 and P3 aliquots, packed in sufficient solid CO_2, will be shipped by an authorised courier from the clinical Phase I Unit, Switzerland, to Anapharm, Spain. P1 and P3 aliquots will remain stored at the analytical laboratory up to finalisation of the bioanalytical report and, in any case, no longer than final CSR finalisation. Afterwards, the samples will be destroyed, and a certificate of destruction will be provided to the Sponsor.

The counter-samples (P2 and P4 aliquots) will remain stored at CROSS Research S.A., Switzerland. These samples could either be:

- sent to the laboratory for reanalysis should this become necessary for analytical reasons or if any problems occur during the delivery of P1 and P3 aliquots, or
- destroyed at an authorised site, or
- transferred to the sponsor upon written request, or
- sent to a different laboratory for reanalysis should this become necessary for analytical reasons
- samples shall only be stored for as long as strictly necessary for the study's performance (until CSR finalization).

No analyses different from those stated in this protocol and agreed by the subjects when signing the informed consent form will be performed unless a new informed consent and a new approval from the Ethical Committee is obtained.

9.4.2.3 Analytical method

The concentration of Nebivolol and Ramipril/Ramiprilat in plasma samples will be determined at Anapharm, Spain, using a fully validated LC/MS/MS method.

Analyses will be performed according to the general Principles of "OECD Good Laboratory Practices for testing of chemicals" C(81) 30 (final) and GCP.

The method validation report and the analytical report will be attached to the final report.

9.4.3 Assessment of Safety

The following assessments will be performed to monitor subjects' safety along the study at specific time points according to the study flow-chart (§ 2.2).

9.4.3.3 Physical examination and vital signs.

Physical examination will be performed and vital signs will be measured according to study flowchart (§ 2.2).

Physical examination will be performed by a Research Physician and will include: ear / nose / throat, ophthalmological, dermatological, cardiovascular, respiratory, gastrointestinal, neurological, lymph nodes, musculoskeletal system, height (in cm) and weight (in kg) measurement. Other body systems can be examined if required, at the discretion of the Investigator.

The following vital signs parameters will be measured: Frontal body temperature (in °C), DBP and SBP (in mmHg), PR (in pulse/minute) and RR (in breaths/minute). SBP, DBP, PR and RR (body temperature and RR only at screening, pre-dose and at EOS visit) have to be measured after at least 10-minute rest in supine position. At screening, BP should be measured also after 2 to 5 minutes of standing to evaluate orthostatic hypotension .

Unscheduled physical examinations and vital signs can be performed for safety reasons, according to the Investigator's judgement.

Clinically significant abnormal findings detected in physical examination or vital signs after the signature of the ICF will be reported as AEs in the eCRF.

9.4.3.4 Clinical Laboratory Evaluation

Safety laboratory tests to be conducted at different time points (see § 2.2) are listed below:

Biochemistry: Sodium, potassium, chloride, total calcium, glucose, creatinine, urea, total protein, albumin, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), creatinine phosphokinase (CPK).

Haematology: Red blood cell (RBC) count, haematocrit (HCT), haemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red blood cell distribution width (RDW), white blood cells (WBC) and differential WBC count (neutrophil, lymphocyte, monocyte, eosinophil and basophil count, absolute), platelet count and Mean platelet volume (MPV).

Serology: HIV-1, HIV-2, hepatitis B (i.e., HBsAg and HBcAb), hepatitis C.

Drugs of abuse: Urinary drug 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).

Urinalysis: pH, density, proteins, glucose, ketones, nitrite, bilirubin, urobilinogen, haemoglobin, leukocyte esterase (leukocytes), colour. Urine sediment assessment is performed if the dipstick test is positive for blood or/and protein.

Pregnancy test on females of childbearing potential: β-HCG in serum at screening and using a dipstick in urine at each Admission to the clinical centre.

Alcohol test: salivary tests to detect alcohol consumption.

Cotinine urine test: urine test to detect tobacco consumption.

Genotyping test for CYP2D6: normal, ultra-rapid, intermediate and poor metabolizers will be identified from the analysis of peripheral blood. This test will be performed at Unilabs Ticino, Switzerland, only in case this data is not available yet from past studies carried out at the clinical unit.

Unscheduled laboratory tests can be performed for safety reasons according to the Investigator's judgement.

Analysis of biochemistry, haematology, urinalysis, virus serology tests and serum pregnancy test at screening will be done at Unilabs Ticino, Switzerland, following local standard laboratory procedures.
Cotinine urine test, alcohol salivary test, drug of abuse test and urine pregnancy test will be done at the clinical centre, following local standard laboratory procedures.
The reference ranges of laboratory parameters described in this study will be submitted by the site to the Sponsor, prior to beginning of the study and will be updated as appropriate.
The lab reports should be identified with the subject number, as well as the date and time of sample collection.
All results should be reviewed by the Investigator with reports being dated and signed by the Investigator and stored in the subject's record.
Clinically relevant abnormal findings detected after the signature of the ICF will be reported as AEs in the eCRF.

9.4.3.5 12-Lead ECG

The 12-lead ECGs will be performed after at least 10-minute rest in supine position as reported in the study flow-chart (§ 2.2). The ECG report should be identified with subject ID number as well as the date and time of recording.
The dated and signed printed version of the ECG will be regarded as source data.
ECGs may be repeated for quality reasons and the results of the repeated ECG will be analysed.
Unscheduled ECGs may be collected by the Investigator for safety reasons. Any abnormalities in the cardiac conduction, depolarisation, repolarisation, arrhythmic events and other abnormalities will be evaluated for their clinical or not clinical significance by the Investigator or designee.
Clinically relevant abnormal findings detected after the signature of the ICF will be reported as AEs in the eCRF.

9.4.4 Study Endpoints

9.4.4.3 Primary PK parameters

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 formulation).

9.4.4.4 Secondary PK parameters

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

9.4.4.5 Exploratory PK parameters:

AUC from time zero to 72h ($AUC_{(0-72)}$), tmax, λz, $t_{1/2}$ and C_{max} of Ramiprilat when NEB and RAM are administered as Test and Reference formulations.

Other PK parameters for all the analytes can be derived if considered appropriate at the time of the analysis.

9.4.4.6 Safety parameters

Incidence, intensity (severity), seriousness and treatment causality of Treatment Emergent Adverse Events (TEAEs, i.e. AEs that occur after the first study drug intake).

9.5 Adverse Event Definitions, Monitoring / Recording and Management

9.5.2 Applicable SOPs

AEs definition, classification and management will follow the Sponsor SOPs, based upon applicable local and international regulations.

9.5.3 Definitions

9.5.3.3 Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

NOTE 1: A Clinical Event stands for any clinical condition, not associated with a drug intake, prior to IMP administration that occurs for the first time or worsens after signing the informed consent.
NOTE 2: A Treatment-Emergent Adverse Event (TEAE) stands for an AE that occurs for the first time or that worsens in terms of seriousness or severity after the first study drug intake.

9.5.3.4 Drug Relationship

The relationship between an AE and study drugs will be judged according to the following categories:

1. **Certain:** The AE occurs in a plausible time relation to the administration of the drug and cannot be explained by a concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge (AE reappearance after drug reintroduction) procedure if necessary.

2. **Probable:** The AE occurs in a reasonable time relation to the administration of the drug, it is unlikely to be attributed to a concurrent disease or other drugs or chemicals and it follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information (AE reappearance after drug reintroduction) is not required to fulfil this definition.
3. **Possible:** The AE occurs with a reasonable time relation to the administration of the drug, but it could also be explained by a concurrent disease or other drugs or chemicals. Information on drug withdrawal (dechallenge) may be lacking or unclear.
4. **Unassessable:** The relationship cannot be judged, because the information is insufficient or contradictory and cannot be supplemented or verified.
5. **Unlikely:** A causal relationship cannot be definitively ruled out, but other drugs, chemicals, or underlying disease provide plausible explanations and/or the temporal relation to the administration of the drug makes a causal relation improbable.
6. **Not Related:** Any of the following are present:
    - existence of a clear alternative explanation, and/or;
    - unreasonable temporal relationship between drug and event, and/or;
    - non-plausibility.

9.5.3.5 Adverse Drug Reactions (ADRs)

An ADR is any untoward and unintended response to an Investigational Medicinal Product (IMP) administered.

The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

An ADR is considered any AE for which the relationship is considered as:

1. Certain
2. Probable
3. Possible
4. Unassessable

An AE is not considered as ADR when the relationship is judged as:

5. Unlikely
6. Not related

9.5.3.6 Seriousness

An AE/ADR is considered serious when:

- results in death;
- is life-threatening;

NOTE: *Life-threatening is considered any AE in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is another medically important condition that may jeopardise the subject or may require intervention to prevent one of the outcomes listed above. Any suspected transmission of an infectious agent via a medicinal product is considered serious and

should be assessed under the category of medically important events in the absence of other seriousness criteria.

A Serious Adverse Event (SAE)/ Serious Adverse Reaction (SAR) is considered as serious when it fulfils at least one of the conditions for the definition of seriousness.

An AE/ADR is considered **non-serious** when it does not fulfil the conditions for the definition of serious AE/ADR.

9.5.3.7 Adverse Event (AE) / Adverse Drug Reaction (ADR) Intensity (Severity)

The intensity level of a serious or a non-serious AE or ADR is attributed according to the following definitions:

- **Mild:** does not interfere with routine activities; in case of laboratory tests, when there is a mild abnormality.
- **Moderate:** interferes with the routine activities; in case of laboratory tests, when there is a moderate abnormality.
- **Severe:** makes it impossible to perform routine activities; in case of laboratory tests, when there is a significant abnormality.

9.5.3.8 Adverse Event (AE) / Adverse Drug Reaction (ADR) Expectedness

An AE/ADR is considered **unexpected** when the nature, severity, or outcome of the AE/ADR is not consistent with the information provided in the safety sections of the Investigator Brochure (IB), which includes as the Reference Safety Information (RSI) the information of the Summary of Product Characteristics (SmPC) of Nebivolol (Nebilet® 5 mg tablet) [6] and Ramipril (Cardace®10 mg tablet) [7].

The definition of ADR also covers medication errors and uses outside what is foreseen in the protocol, including overdose, misuse and abuse of the product.

9.5.3.9 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any serious adverse event judged by the Investigator or the Sponsor as drug-related, i.e. Serious Adverse Reaction (SAR; see § 9.5.1.4) and unexpectedly qualifies as a Suspected Unexpected Serious Adverse Reaction (SUSAR). As a general rule for this clinical study, all SARs should be considered unexpected even if listed in the SmPCs of Nebivolol (Nebilet® 5 mg tablet) and/or Ramipril (Cardace® 10 mg tablet) or even if a SAR of the same kind has already previously occurred during the clinical study.

Therefore, all SARs occurring in the clinical study NEB-RAM-01 will be processed in accordance with the applicable regulations for SUSARs. SUSARs are subject to expedited reporting, as specified in § 9.5.3.2, as having a "Reasonable Possibility" of relationship with the IMP.

In case of any SAR, subject enrolment and treatment administration will be put on-hold or stopped. The study will be resumed only after specific discussion and agreement with the IEC and the CA.

9.5.3.10 Individual Case Safety Report (ICSR)

Format and content provided to describe one or several AEs or a disease experience that occurs to an individual subject at a particular point of time.

9.5.4 Collection, recording and reporting of Adverse Events

At each visit, the Investigator will collect, assess and record in the eCRF any occurred subjective or objective AE and clinical event occurred to each subject after his/her signature of the informed consent.

The Investigator should manage as AE any laboratory test abnormality (newly occurring after the IMP administration or worsening of previously known abnormalities) considered as clinically significant: i.e., values significantly above or under normal range or which require an intervention or diagnostic tests, or may result in the IMP discontinuation.

SARS-CoV-2 infection (either asymptomatic or symptomatic as COVID-19) will be recorded as an adverse event. Suspected cases should always be confirmed by molecular testing (RT-PCR).

Any AE communicated by the subject or by the subject's relatives or delegates through phone calls, letters or emails will also be recorded and assessed. In these cases, the Investigator will try to obtain medical confirmation and assessment of the occurred AE.

When an AE has occurred, the Investigator shall record it on the respective eCRF-AE pages. This applies to both serious and non-serious cases, whether or not thought to be drug-related, observed in or reported by the subject (or relatives/delegates), specifying the judgement on the causal relationship with the study treatment. When the investigator confirms that all the collected information on any ICSR (serious or not, related or not) has been entered in the eCRF on the case summary page, an email notification will be sent to the Sponsor.

The Investigator is expected to record any AE occurring during the study follow-up period until the End of Study visit, too.

Moreover, the Investigator is expected to follow-up any AE which leads to discontinuation and any ongoing SAE occurred during the study, until the outcome has been determined (for details, please see § 9.5.9).

Any available relevant information and/or diagnostic measure (laboratory and instrumental tests, procedures, etc.) shall also be recorded in the e-CRF AE pages.

9.5.5 Management of Serious Adverse Events (SAEs) including laboratory abnormalities

9.5.5.3 Reporting Duties of the Investigator

The Investigator must report all the available information concerning any SAE and any severe AE (whether or not thought to be related to any of the investigational product) by completing the eCRF AE pages **no later than 24 hours** after the first knowledge of its occurrence.

Once the information is validated in the eCRF, a notification e-mail will be automatically generated and sent to the Sponsor's SDSM (Study Drug Safety Manager) so that the SAE or severe AE can be retrieved.

The Investigator will be provided with the paper CRF-SAE form to be used for SAE or severe AE only in case of breakdown of the eCRF system. In such a case, the Investigator will be

responsible for sending the paper CRF-SAE form and inserting the data in eCRF as soon as the system works again.
Whenever the paper CRF-SAE form is used, it must be submitted by e-mail to the SDSM:

SDSM contact details:
Dr. Isabel Paredes Lario
Alfonso XII, 587
08918 Badalona (Barcelona)
Spain
Phone: +34 93 463 32 66 (working hours)
Mobile: +34 606 78 61 40
e-mail: sdsu@menarini.es

For the initial SAE/ severe AE, the Investigator should enter at least the following data:

- AE medical term.
- Seriousness criteria.
- Causality assessment.
- Study Code and Subject Identification (subject ID) [when the paper CRF-SAE form is used].
- Reporter's name and telephone number for clarification [when the paper CRF-SAE form is used].

The Sponsor's confirmation of reception of the SAE report / severe AE report must be kept in the subject's records.

Any questions that arise during the processing and medical review of the SAE/ severe AE report will be managed by means of electronic queries (i.e., queries in the eCRF). In case of breakdown of the eCRF system, queries will be sent by e-mail.

When relevant, also the eCRF pages concerning medical history, prior and concomitant medications, and laboratory tests will be retrieved by the SDSU.

Any further information and supporting documentation that become available (copies of laboratory reports, tests, procedures, autopsy evidence in case of death, etc.) shall be provided by the Investigator to the Sponsor's SDSM by e-mail no later than 24 hours after knowledge.

The Investigator must also comply with the local applicable obligation(s) on the reporting of ADRs to the local concerned Regulatory Authority/Ethics Committee, if any.

9.5.5.4 Reporting Duties of the Sponsor

The Sponsor shall ensure that all relevant information about any SUSAR, is expeditiously reported to the Regulatory Authorities (EC and CA) with the following deadlines after the first knowledge, intended as the day when the SDSM or CRO receives the first information of the SUSAR:

- Fatal and life-threatening unexpected cases: no later than 7 days;
- Other unexpected serious cases: no later than 15 days.

The Sponsor shall ensure that all relevant new information and supporting documentation that subsequently becomes available, is also expeditiously reported as follow-up information no later than 15 days after the first knowledge for all cases.

Furthermore, the following safety issues will be subject to expedited management for the identification of possible necessary actions:

- SAEs associated with the trial procedures,
- potential clinically significant findings emerging from non-clinical studies,
- an anticipated end or suspension for safety reasons of another trial with the same study drug/s.

When appropriate and applicable, the Sponsor will arrange the adequate information also to the Investigator

9.5.6 Management of Non-Serious Adverse Events (NSAEs) including laboratory abnormalities

9.5.6.3 Reporting Duties of the Investigator

The Investigator must record all the available information concerning any case with a NSAE (whether or not deemed related to the investigational drug) in the eCRF-AE pages in a timely manner, preferably no later than 5 calendar days after the first knowledge of occurrence. When a new AE is entered, a notification email will be automatically generated and sent to the SDSM, in order that the NSAE can be retrieved.

When relevant, also the eCRF pages concerning medical history, prior and concomitant medications, and laboratory tests will be retrieved by the SDSM for the evaluation of the case. Any further information and supporting documentation that become available (copies of laboratory reports, tests, procedures, etc.) shall be entered by the Investigator in the eCRF no later than 24 hours.

The site must also comply with the local applicable obligation(s) on the reporting of serology and SARS-CoV-2 test results.

9.5.6.4 Management of any laboratory abnormality and other safety parameters

In addition, during the clinical study, abnormalities in laboratory analyses, urinalysis, physical examination, vital signs or 12-lead ECG (newly occurring after ICF signature or worsening of previously known abnormalities), which are considered as clinically significant by the Principal Investigator (such as values significantly above or under normal range or which require an intervention or diagnostic tests, or may result in the discontinuation of the study treatment), should be reported as AEs.

All abnormalities in laboratory values will be periodically collected and reviewed by the Sponsor at least on a monthly basis.

9.5.7 Management of Pregnancy Exposure Cases

The Investigator is expected to record in the dedicated paper "Pregnancy Exposure Report Form" any case of pregnancy exposure, occurring in a female subject or in a subject's partner enrolled in the study, occurring during the course of the study.

The "Pregnancy Exposure Report Form" is distributed to the site to be used for this purpose. The mentioned form will be sent by e-mail to the Sponsor's SDSM within 5 days after the investigator is aware of the pregnancy, and it is also to be fully completed and sent again within 5 days after the outcome is known.

In case of pregnancy, the subject will be withdrawn from the study. The Investigator is requested to follow each case of pregnancy exposure until the outcome, provided that the female subject or the subject's partner enrolled in the study has signed the related pregnancy ICF.

If the pregnancy results in an abnormal outcome, this will be recorded in the eCRF (if still available) as a SAE and managed as described above (§ 9.5.3.1). In case the eCRF is no longer available, it will be notified through the paper CRF-SAE form and sent to the Sponsor's SDSU by e-mail.

9.5.8 Management of cases of misuse and overdose

Although study drug misuse and overdose are not considered AEs per se, those issues should be reported to the Sponsor's SDSU within 24 hours of knowledge, even if they may not result in an adverse outcome. In the event of any such occurrence, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
For the purpose of this protocol, the following definitions apply:

- A case of misuse describes situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of current protocol.
- An overdose is any dose of the investigational drugs (Nebivolol or Ramipril) which is more than the assigned dose level for that subject.

The corresponding information should be entered in the AE page in the eCRF **no later than 24 hours** from awareness by the site. Once the page is completed and saved by the staff involved in the study, an alert notification will be automatically sent to the Sponsor's SDSM. ONLY if the eCRF system does not work or if the eCRF is not available, the paper SAE report form shall be used and sent to the Sponsor by email.

In addition, if an AE (serious or non-serious) is associated with an overdose, it will be recorded on the AE page in the eCRF, recording the overdose details.

If the pharmacy service discovers that an overdose has or may have been administered, they should immediately contact the Investigator and Sponsor (or their delegate) and let them know.

9.5.9 Annual Safety Reporting

In general, once a year throughout the clinical trial, the Sponsor should assure the submission to the concerned CA and IEC of a safety report (Development Safety Update Report, DSUR), considering all new safety information received during the reporting period. DSUR will be submitted to CAs and ECs by the SDSU within 60 calendar days after the Data Lock Point

(DLP). The above will not be applicable to this study provided that its duration is less than a year.
The IB in force at the start of the reporting period should serve as the reference safety information for the document preparation.

9.5.10 Serious and Non-Serious Adverse Events Follow-up

After the End of Study Visit, the Investigator is not requested to actively follow-up the subject unless the following events are present: AEs which led to discontinuation, non-serious AEs of special interest or serious AEs still ongoing. In these cases, the event/s will be followed until the event disappears or the subject's conditions stabilise unless the subject is lost to follow-up. However, if the Investigator becomes aware of a SAE with a suspected causal relationship to the study treatment that occurs to a subject treated by him or her after the end of the clinical trial, the investigator shall, without undue delay, report the SAE to the Sponsor. These SAEs occurred after End of Study Visit should be also recorded in the eCRF until it is available, if the eCRF is not available anymore, the paper CRF-SAE form will be used as a backup and sent to the SDSU by email whenever possible.

10 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

10.1 Determination of Sample Size

A sample size of 42 subjects (14 subjects per each of the sequences A, B and C) is considered adequate for testing the bioequivalence between NEB/RAM 5/10 mg FDC (Test formulation) and NEB 5mg + RAM 10 mg EC (Reference formulation) at 5% (one side) level of significance with a power higher than 80% based upon a Test versus Reference ratio varying between of 0.95 and 1.05 and an intra-subject coefficient of variation of a maximum of 36.2%. [(1), (2)]
In order to account for approximately a 22% of potential dropouts during the clinical phase and exclusions from the PK population, twelve extra subjects will be included into the study and a total number of 54 subjects will be randomized.

10.2Analysis Populations

Safety population: All subjects receiving 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.

10.3 Statistical Analysis

10.3.1 Descriptive statistics

All study variables will be presented by treatment and overall, by using the appropriate descriptive statistics according to the variable nature, unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, standard error of the mean, minimum, median, maximum.

- Categorical variables: number of non-missing observations and column percentages (N, %).
- PK parameters: arithmetic mean, SD, Coefficient of Variation (CV%), geometric mean (GM), geometric SD, geometric CV% and its 90% confidence interval (CI), minimum, median and maximum.

Results will be presented by study populations, as appropriate.
When estimating the mean or median value for the concentration at a given time point (descriptive mean or median curve), a value of 0 will be assigned to below LLOQ (BLOQ) values. The mean/median value at a time with one or more BLOQ values will be reported (in tabular or graphical fashion) unless the mean/median value is below the LLOQ of the assay, in which case the value will be assigned BLOQ.
All the baseline characteristics will be summarized through descriptive statistics.

10.3.2 Pharmacokinetic analysis

The PK analysis will be run on the PK population. All PK parameters will be summarized by descriptive statistics as detailed in § 10.3.1.
Individual concentration versus time profiles (linear and semi-log scales) for Nebivolol, Ramipril and Ramiprilat will be graphically displayed by subject and treatment as appropriate.

10.3.3 Analysis of primary PK parameters

For bioequivalence testing 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 will be analysed by means of mixed effect model including sequence, period, formulation and subject within sequence as fixed effects, and taking into account the partial replicate design.
Estimates of the mean difference (Test formulation – Reference formulation) and corresponding 90% CIs will be obtained from the model for each analyte.
The mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of geometric means (Test formulation/Reference formulation) and 90% corresponding CIs.
Bioequivalence will 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 NEB and RAM C_{max} and $AUC_{(0-t)}$ fall wholly within the bioequivalence acceptance range (80.00% to 125.00%).

Intra-subject variability of Ramipril C_{max} has been reported > 30%, suggesting that Ramipril might be a highly variable drug product. Thus, according with the EMA guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) [(9)], the bioequivalence acceptance limits for Ramipril C_{max} can be widened to a maximum of 69.84 – 143.19% in case the observed intra-subject CV% for the reference is confirmed as > 30%, according to the formula:

$$[U, L] = \exp [\pm k \cdot sWR]$$

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 $\sqrt{ln(CV^2+1)}$.

10.3.4 Analysis of secondary PK parameters

The following secondary PK variables for the analytes Nebivolol and Ramipril will be compared when administered as FDC tablet vs. EC:

- $AUC_{(0-\infty)}$ will be analysed similarly to $AUC_{(0\text{-}t)}$.
- Other PK parameters will be summarized descriptively.

10.3.5 Analysis of Exploratory PK variables

Exploratory PK parameters will be summarized descriptively. The bioequivalence testing may be required for Ramiprilat as well in case of inconclusive results of the BE based on Ramipril.

10.3.6 Safety Analysis

The safety analysis will be run on the safety population and will encompass AEs, laboratory tests, physical examination, vital signs and 12-lead ECG data. It will be carried on by using descriptive statistics.

- AEs will be coded according to the last version of the MedDRA available at the start of the study.
- TEAEs will be presented by treatment/sequence and tabulated by causal relationship, intensity, seriousness and discontinuation of treatment. TEAEs will be also summarised by primary System Organ Class (SOC) and preferred term (PT). For each PT / SOC, number of TEAEs, number and percentage of subjects with TEAE will be overall listed and stratified by intensity (mild, moderate and severe) and by their relationship to the study drugs (related/not related).
- SAEs will be analogously analysed as TEAEs.
- ADRs will be analogously analysed as TEAEs.
- AE/SAE not considered TEAE will be included in a separate listing
- Other Safety Variables: Descriptive statistics for absolute value and change (versus baseline, i.e. last assessment prior to dosing) of vital signs, 12-lead ECG, physical examination, laboratory tests will be presented by time point, sequence and overall.

10.3.7 Data imputations

The missing values will not be imputed because an observed-cases approach will be applied.

10.4 Protocol Violations and Data Review

Categories of protocol violations will be properly defined and will be integrated in the statistical analysis report.
Subjects with violations that have an impact on the PK analysis will be excluded from the PK population. For other types of violation, a subject listing will be provided only for exploratory purposes.

10.5 Statistical Analysis Plan

The statistical analysis plan (SAP) will be finalised before the first subject in. The SAP will describe in detail study endpoints and the statistical analyses, including the statistical analysis

of the primary endpoint, as well as additional endpoints and analyses not planned in the protocol. In case of change of the original primary endpoint or of the original primary analyses will occur during the study, these changes will be the subject of a substantial protocol amendment.
Minor deviations (e.g., not involving changes in the primary endpoint and analysis) which might occur during the study will be detailed only in the SAP. All statistical analyses not pre-specified will be considered additional/exploratory analyses.
Protocol deviations (missing assessments/visits) related to COVID-19 will be listed separately (if appropriate).

11 DATA QUALITY MANAGEMENT

11.1 Data Collection

Data collection activities will be carried out under the responsibility of the Sponsor.

Subject data will be collected using the data capture systems described below.
Subjects will be identified by subject number assigned at the screening visit.
In addition, a randomisation number will be assigned to each subject as soon as eligibility to the study is confirmed at the PK Session 1.
The data will be collected, processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations.

11.1.1 Electronic Case Report Forms

Clinical data collected during the study at sites will be recorded in SD and transferred into an eCRF using Medidata Rave which is a validated system and 'Title 21 CFR Part 11' compliant. The eCRF will be developed based on this study protocol under the responsibility of the Sponsor.
The Investigator or designee will be responsible for entering study data into the eCRF in accordance with the eCRF Completion Instructions provided by the Sponsor. In order to improve the quality of data collection and cleaning, data shall be entered into the eCRF as closely as possible to the time when they become available and not later than within 5 working days (24h for SAEs and severe AEs as well as cases of misuse and/or overdose, as mentioned elsewhere). The eCRF data will not be considered as source data (the definition of the source data can be found in § 11.3).
Investigators will ensure the accuracy, completeness and consistency of data entered, signing electronically the eCRF using the personal password.
An audit trail within the system will track all changes made to the data.

11.1.2 Analytical laboratory data

For every activity performed by the analytical laboratory, the relative procedures regarding collection, shipment and/or retention of samples will be detailed in the corresponding laboratory manual. The transfer of data to the Sponsor will be regulated with a dedicated Data Transfer Agreement (DTA).

11.1.2.1 PK Laboratory data

Analytes concentrations will be provided according to the specifications defined in the data transfer agreement between the CRO and the sponsor.

11.1.2.2 CYP2D6 Laboratory data

Results of the CYP2D6 analysis will be provided according to the specifications defined in the data transfer agreement between the analytical laboratory and the site.

11.1.2.3 Data Capture System Versions and Validation Documentation
The Sponsor will maintain a list of the data capture system versions used and the validation documentation of each version. The validation documentation will be provided to the site upon request (e.g., in case of audits or inspections).

11.2 Clinical Data Management

Data Management will be carried out under the responsibility of the Sponsor. eCRF data will be electronically verified through the use of on-line and off-line checks. Discrepancies in the data will be resolved by means of electronic queries. Data will be locked by the Sponsor clinical data manager when all activities for the trial, including medical revision of the data, are complete and no more entries are expected.
Data from sources other than eCRF will be provided to the clinical data manager on an agreed scheduled basis. The Sponsor clinical data manager has the responsibility to reconcile data captured in the eCRF, with external data sources. Discrepancies found in the reconciliation of the data will be addressed by means of queries.
A clear overview of all clinical data management activities will be given in the clinical data management plan.

11.3 Source Data

Source data are defined as all data in original records or certified copies of original records of clinical findings, observations or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.
Original documents and data records include, but are not limited to clinic / subject' medical records, laboratory notes, ECG records, subject' identification forms, and pharmacy dispensing records. Study sites will also maintain paper drug accountability forms for the study treatments to document dispensation and return.
Source data should be held available for perusal by the Sponsor representatives of the study or to other authorised persons such as auditors and inspectors of Regulatory Authorities.
Direct access to source data is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important for evaluation of a clinical trial (see also § 11.4.1) Any party allowed to direct access to study source data and documents should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of subject identities and sponsor proprietary information.

Data should be consistent with the source documents and discrepancies, if any, should be explained in writing. All the original documentation pertinent to the study procedures must be available for review in each subject's record.

11.4 Quality Assurance and Quality Control

11.4.1 Study Monitoring

This trial will be monitored in accordance with the ICH Note for Guidance on GCP. Monitoring will be carried out under the responsibility of the CRO. The site monitor will perform visits to the trial site along the study conduct. Facilities, study drug, storage area, eCRF, subject's source

data, and all other study documentation will be inspected/reviewed by the site monitor for adherence to the protocol and GCP.
At each site visit, the monitor will review the eCRFs for completion and accuracy. Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and his/her staff. The Investigator agrees to allow access to all study related materials needed for the proper review of study conduct and to assist the monitor during the monitoring visits and during the data cleaning process. Monitoring procedures require that 100% of data are source data verified or a risk-based monitoring (if applicable), particularly focusing on informed consents, adherence to inclusion/exclusion criteria, drug accountability, documentation of SAEs and the proper recording of PK sampling time-points and safety measurements. All monitoring activities will be described in detail in the study-specific Monitoring Plan.

11.4.2 Quality Assurance

Independent study audit(s) and / or inspection(s) may take place at any time during or after the trial. The independent audit / inspection can be carried out by the Quality Assurance (QA) of the CRO, the QA Department of Menarini Ricerche S.p.A., or a Competent Authority. At all times, the confidentiality of subject related documents will be maintained.

12 PREMATURE TERMINATION OF THE WHOLE STUDY

The whole trial may be discontinued at the discretion of the Sponsor in the event of any of the following:

- New information leading to favourable risk-benefit judgement of the investigational products due to:
  - Occurrence of significantly previously unknown AEs or unexpectedly high intensity or incidence of known AEs;
  - New evidence of unfavourable safety or efficacy findings (from clinical or non-clinical examinations, e.g. toxicology).
- New data become available regarding COVID-19 which raise concern for the safe study conduct so that continuation would pose potential risks to the subjects or the study site staff.
- The Sponsors decision that continuation of the trial is unjustifiable for medical or ethical reasons;
- Discontinuation of development of the IMP.

CAs and IECs will be informed about the discontinuation of the trial in accordance with applicable regulations.

13 END OF CLINICAL TRIAL AND ARCHIVING

The clinical trial will end with the collection and analysis of study data and the issue of the clinical study report. All essential documents will be archived by the Sponsor and the Site according to the relevant SOP.

13.1Archiving of electronic documentation/data

As described in § 5.5, duplicate electronic media such as CDs/DVDs (one for routine access and one for back-up) containing the subject data in PDF format (e.g., eCRFs) for the site will be prepared by the Sponsor or a delegate for archiving purposes. The electronic media, of a not re-printable type, will be appropriately labelled recording the files/data included. The files should contain at least the eData copy clearly reporting the system name, study code and the eCRF version used; for eCRF data also the electronic signature and the associated audit trails have to be included.
The Investigator should verify whether the provided electronic media represent a complete copy of eCRFs generated during the study. The investigator has to confirm the receipt and correctness of the material by signing a dedicated form provided by the Sponsor, the signed form has to be collected and archived in the TMF. The Sponsor will sent to the Investigator fresh copies of the media approximately every 7 years to ensure long term archiving of files/data..
Two copies of the same electronic media prepared for the site or cumulative electronic media with the same content will be archived by the Sponsor and refreshed approximately every 7 years to ensure long term archiving of files/data. In addition, the Sponsor is responsible to create 2 electronic media (one for routine access and one for back-up) containing an integrated SAS database with all study data (e.g., eCRF), with appropriate refreshment procedures.

14 REFERENCES

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