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(54) **Title:** METHODS AND PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF CARDIAC REMODELING

(57) **Abstract:** The present invention relates to the treatment of cardiac remodelling. In this study, the inventors demonstrated, using male Wistar rats submitted either to sham surgery or ligation of left anterior descending coronary artery to cause MI, that oral administration of the vitamin B3 nicotinamide riboside (NR), a precursor for NAD coenzyme that is used in energy metabolism prevents the onset of adverse cardiac remodeling after myocardial infarction and the development of systolic dysfunction. Thus, the present invention relates to the nicotinamide riboside for use in the treatment of cardiac remodeling in a subject in need thereof.

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METHODS AND PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF CARDIAC REMODELING

FIELD OF THE INVENTION:

The present invention relates to the nicotinamide riboside for use in the treatment of cardiac remodeling in a subject in need thereof.

BACKGROUND OF THE INVENTION:

Myocardial infarction (MI), also called a heart attack, is the most current manifestation of ischaemic heart disease or coronary heart disease which is the leading single cause of premature morbidity and death accounting for 9.43 million of deaths (16.6 % of total deaths) in 2016 following the World Health Organization estimates. Despite improvement in pharmacological treatments and aggressive reperfusion strategies, a significant number of patients surviving to an acute MI develop left ventricular dysfunction due to the loss of functional myocardium. These patients develop adverse left ventricular remodelling defined by a progressive dilatation of the left ventricle eventually associated with the formation of ventricular aneurysm (Ibanez et al., 2017). Patients developing this adverse cardiac remodelling are at high risk of developing heart failure (HF).

There is a major interest in studying the mechanisms underlying the alteration of nicotinamide adenine dinucleotide (NAD) homeostasis in the myocardium in diseases leading to heart failure because NAD is both a major redox cofactor in the catabolic reactions of the energy metabolism, notably glycolysis, fatty acid beta-oxidation, ketone bodies oxidation, tricarboxylic cycle and its reduced form NADH a major electron donnor to the mitochondrial respiratory chain allowing the process of oxidative phosphorylation to generate ATP (Mericskay 2016). In addition NAD is the substrate of a number of important signalling enzymes like the sirtuins, the mono-ADPribose transferases and poly- ADPribose polymerases and ADP ribose cyclases regulating energy metabolism, survival pathways and gene expression in cells (Mericskay 2016).

The inventors have previously shown the efficacy of nicotinamide riboside (NR), a new form of vitamin B3 precursor of NAD+ (Trammell et al., 2016), to restore the levels of this coenzyme in the failing heart in a mouse model of non-ischaemic dilated cardiomyopathy induced by deletion of the transcription factor SRF (model SRFHKO) (Diguet et al., 2018), which shows a fall in the rate of NAD in the myocardiu as reported repeatedly in different HF

models (Mericskay 2016, Matasic, Brenner, and London 2018). They have shown in this model SRFHKO firstly that there is repression of the main route of synthesis of NAD + by the enzyme NAMPT but activation of an alternative synthesis route by the NMRK2 kinase which metabolizes the NR, and secondly that the supplementation of mice's food with this vitamin helps preserving cardiac function and limit ventricular remodelling.

It has been shown that NAD levels severely fall in the myocardium following infarction and that administrating NAD decreases the severity of myocardial damage (Zhang et al 2016, Yamamoto et al 2014, Guan et al 2016, Di Lisa et al 2001). NAD as a phosphate positively charged molecule however is poorly absorbed by cells.

Thus, despite current strategies to manage cardiac remodeling, there is still a need for new evidence-based and cost-effective treatments.

SUMMARY OF THE INVENTION:

In this study, the inventors demonstrated, using male Wistar rats submitted either to sham surgery or ligation of left anterior descending coronary artery to cause MI, that oral administration of the vitamin B3 nicotinamide riboside (NR), a precursor for NAD coenzyme that is used in energy metabolism prevents the onset of adverse cardiac remodeling after myocardial infarction and the development of systolic dysfunction.

Thus, the present invention relates to the nicotinamide riboside for use in the treatment of cardiac remodeling in a subject in need thereof. Particularly, the invention is defined by its claims.

DETAILED DESCRIPTION OF THE INVENTION:

A first aspect of the present invention relates to the nicotinamide riboside for use in the treatment of cardiac remodeling in a subject in need thereof.

Particularly, the nicotinamide riboside can be used for preventing cardiac remodeling in a subject in need thereof.

As used herein the term “cardiac remodelling” denotes changes in the size, shape, structure, and function of the heart. This can happen as a result of exercise (physiological remodeling) or after injury to the heart muscle (pathological remodeling). In the case of a pathologic case, cardiac remodelling appears generally after a myocardial infarction (MI), a dilated cardiomyopathy (DCM) a non obstructive cardiomyopathy, a hypertrophic cardiomyopathy, myocarditis, chronic hypertension, congenital heart disease with intracardiac shunting, and valvular heart disease. Cardiac remodelling leads to a dysfunction of the heart

and for example to cardiac ischemia, cardiac fibrosis, heart failure, systolic dysfunction or cardiomyopathy when the cause of the cardiac remodelling is the myocardial infarction.

Thus, the invention also relates to the nicotinamide riboside for use in the treatment of cardiac remodeling in a subject in need thereof wherein the cardiac remodelling has appeared after a myocardial infarction (MI), a dilated cardiomyopathy (DCM) a non obstructive cardiomyopathy, a hypertrophic cardiomyopathy, myocarditis, chronic hypertension, congenital heart disease with intracardiac shunting, and valvular heart disease.

Thus, the invention also relates to the nicotinamide riboside for use in the treatment of ischemia, cardiac fibrosis, heart failure or systolic dysfunction caused by a cardiac remodelling or for use in the treatment of a cardiomyopathy when the cause of the cardiac remodelling is the myocardial infarction in a subject in need thereof.

As used herein, the term "subject" denotes a mammal, such as a rodent, a feline, a canine, and a primate. Preferably, a subject according to the invention is a human.

As used herein, the term "ischemia" or "ischaemia" denotes a restriction in blood supply to tissues, causing a shortage of oxygen that is needed for cellular metabolism (to keep tissue alive).

As used herein, the term "myocardial infarction" has its general meaning in the art and refers to any disease in which blood flow decreases or stops to a part of the heart, causing damages to the heart muscle. MI are clinically classified according to to the presenting electrocardiogram (ECG) into ST segment elevation MI (STEMI) and non-ST elevation MI (NSTEMI). A MI can classified as acute or non-acute MI. Acute MI usually results from the complete or partial blockage of a coronary artery caused by a rupture of an atherosclerotic plaque, or more rarely by coronary artery spasms. Non-acute-MI is caused by non-coronary syndrome cause, which can including acute pulmonary embolism, renal insufficiency, aortic dissection, heart failure, pericarditis, myocarditis, strenuous exercise, rhabdomyolysis, cardio-toxic chemotherapy, high-frequency ablation therapy, defibrillator shocks, cardiac infiltrative disorders (e.g., amyloidosis), chest trauma, sepsis, shock, exacerbation of chronic obstructive pulmonary disease and diabetic ketoacidosis.

As used herein, the term "cardiomyopathy" has its general meaning in the art and refers to any disease of the heart muscle. Cardiomyopathy can be acquired or inherited. Common symptoms include dyspnea and peripheral oedema, and risks of having dangerous forms of irregular heart rate and sudden cardiac death are increased. Cardiomyopathy often leads to progressive heart failure, i.e the incapacity of the cardiac pump to maintain sufficient blood flow to meet the basal bodily needs for oxygen. The main types of cardiomyopathy include

dilated cardiomyopathy, hypertrophic cardiomyopathy, non-obstructive cardiomyopathy, restrictive cardiomyopathy, left ventricular non-compaction, arrhythmogenic right ventricular cardiomyopathy. Dilated cardiomyopathy is characterized by dilatation and systolic dysfunction of the left or both ventricles. The ventricular walls become thin and stretched, compromising cardiac contractility and ultimately resulting in poor left ventricular function. In one embodiment, the cardiomyopathy is dilated cardiomyopathy. Hypertrophic cardiomyopathy is characterized by the thickening of the left ventricular wall, and/or the interventricular septum, or just one region of the ventricle. Cardiac remodeling triggered by myocardial infarction can lead to hypertrophy of the surviving myocardium, or remote myocardium, intersticial fibrosis. Cardiac remodeling triggered by myocardial infarction is also associated with the formation of a fibrous scar replacing the dead myocardium. The fibrous scar alters ventricular mechanics contributing to systolic and or diastolic dysfunction. Cardiac remodeling triggered by myocardial infarction can also lead to ventricular aneuryms, a bulge or 'pocketing' of the cardiac wall, a dangerous condition increasing the risk of myocardial rupture. In one embodiment, the cardiomyopathy is rare cardiomyopathy.

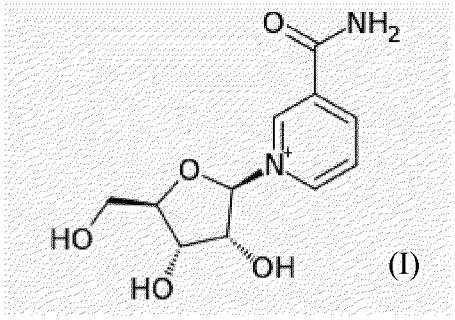
In one embodiment, the rare cardiomyopathy is one life-threatening symptom among several in complex disorders and is selected but not restricted from the group consisting of Congenital cardiomyopathy, Emery Dreiffuss Muscular Dystrophy, Duchenne and Becker Muscular Dystrophy, Limb-Girdle dystrophy, Steinert disease, Danon disease, Myofibrillar Myopathy, Arrhythmogenic dysplasia, Peripartum cardiomyopathy, Tako Tsubo cardiomyopathy, Nemaline Myopathies or RASopathies.

As used herein, the term "treatment" or "treat" refer to both prophylactic or preventive treatment as well as curative or disease modifying treatment, including treatment of patients at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition, and includes suppression of clinical relapse. The treatment may be administered to a patient having a medical disorder or who ultimately may acquire the disorder, in order to prevent, cure, delay the onset of, reduce the severity of, or ameliorate one or more symptoms of a disorder or recurring disorder, or in order to prolong the survival of a patient beyond that expected in the absence of such treatment. By "therapeutic regimen" is meant the pattern of treatment of an illness, e.g., the pattern of dosing used during therapy. A therapeutic regimen may include an induction regimen and a maintenance regimen. The phrase "induction regimen" or "induction period" refers to a therapeutic regimen (or the portion of a therapeutic regimen) that is used for the initial treatment of a disease. The general goal of an induction regimen is to provide a high

level of drug to a patient during the initial period of a treatment regimen. An induction regimen may employ (in part or in whole) a "loading regimen", which may include administering a greater dose of the drug than a physician would employ during a maintenance regimen, administering a drug more frequently than a physician would administer the drug during a maintenance regimen, or both. The phrase "maintenance regimen" or "maintenance period" refers to a therapeutic regimen (or the portion of a therapeutic regimen) that is used for the maintenance of a patient during treatment of an illness, e.g., to keep the patient in remission for long periods of time (months or years). A maintenance regimen may employ continuous therapy (e.g., administering a drug at a regular intervals, e.g., weekly, monthly, yearly, etc.) or intermittent therapy (e.g., interrupted treatment, intermittent treatment, treatment at relapse, or treatment upon achievement of a particular predetermined criteria [e.g., disease manifestation, etc.]).

As used herein, the term “nicotinamide riboside” (NR) has its general meaning in the art and refers to a pyridine-nucleoside form of vitamin B3 that is a precursor to nicotinamide adenine dinucleotide or NAD+. Molecular formula of nicotinamide riboside is $C_{11}H_{15}N_2O_5^+$. The term “nicotinamide riboside” includes any derivative of nicotinamide riboside.

Nicotinamide riboside formula (I):



(I)

The invention also relates to a method for treating cardiac remodeling in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of nicotinamide riboside.

Pharmaceutical composition

Another object of the invention relates to a therapeutic composition comprising nicotinamide riboside according to the invention for use in the treatment of cardiac remodeling in a subject in need thereof.

Any therapeutic agent of the invention may be combined with pharmaceutically acceptable excipients, and optionally sustained-release matrices, such as biodegradable polymers, to form therapeutic compositions.

"Pharmaceutically" or "pharmaceutically acceptable" refers to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to a mammal, especially a human, as appropriate.

A pharmaceutically acceptable carrier or excipient refers to a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetables oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminium monostearate and gelatin. In the pharmaceutical compositions of the present invention, the active ingredients of the invention can be administered in a unit administration form, as a mixture with conventional pharmaceutical supports.

The form of the pharmaceutical compositions, the route of administration, the dosage and the regimen naturally depend upon the condition to be treated, the severity of the illness, the age, weight, and sex of the patient, etc.

The pharmaceutical compositions of the invention can be formulated for a topical, oral, intranasal, parenteral, intraocular, intravenous, intramuscular or subcutaneous administration and the like.

Preferably, the pharmaceutical compositions contain vehicles which are pharmaceutically acceptable for a formulation capable of being injected. These may be in particular isotonic, sterile, saline solutions (monosodium or disodium phosphate, sodium, potassium, calcium or magnesium chloride and the like or mixtures of such salts), or dry, especially freeze-dried compositions which upon addition, depending on the case, of sterilized water or physiological saline, permit the constitution of injectable solutions.

The doses used for the administration can be adapted as a function of various parameters, and in particular as a function of the mode of administration used, of the relevant pathology, or alternatively of the desired duration of treatment.

In addition, other pharmaceutically acceptable forms include, e.g. tablets or other solids for oral administration; time release capsules; and any other form currently can be used.

Pharmaceutical compositions of the present invention may comprise a further therapeutic active agent. The present invention also relates to a kit comprising an agonist, antagonist or inhibitor of the expression according to the invention and a further therapeutic active agent as described below.

In some embodiments, nicotinamide riboside is administrated in combination with a therapeutically effective amount of AMPK activator or/and a therapeutically effective amount of PPARα agonist.

In some embodiments, nicotinamide riboside is administrated in combination with a therapeutically effective amount of Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, 3rd generation of beta blocker inhibitors like Carvedilol, hydralazine plus nitrates, aldosterone inhibitors like spironolactone, blood thinners, such as aspirin to break up clots and improves blood flow, thrombolytics to dissolve clots, antiplatelet drugs to prevent new clots from forming and existing clots from growing or nitroglycerin to widen blood vessels..

According to the invention, these further therapeutic active agent can be added to the pharmaceutical composition as described above.

As used herein, the term “AMPK” (5' adenosine monophosphate-activated protein kinase) has its general meaning in the art and refers to AMP-activated protein kinase. AMPK is an energy sensor protein kinase that plays a key role in regulating cellular energy metabolism. In response to reduction of intracellular ATP levels, AMPK activates energy-producing pathways and inhibits energy-consuming processes. AMPK acts via direct phosphorylation of metabolic enzymes, and by longer-term effects via phosphorylation of transcription regulators.

As used herein, the term “AMPK activator” has its general meaning in the art and refers to any compound, as well as its derivatives and prodrugs, that promotes activity of AMPK directly, or indirectly (for example, any compound that increases intracellular AMP concentration is an AMPK activator) or to any compound that enhances AMPK gene expression,

As used herein, the term “PPARα” has its general meaning in the art and refers to Peroxisome proliferator-activated receptor alpha, also known as NR1C1 (nuclear receptor subfamily 1, group C, member 1). PPARα is a nuclear receptor protein and is a key regulator of lipid metabolism.

As used herein, the term “PPARα agonist” refers to any compound, as well as its derivatives and prodrugs, natural or not, that is able to bind to PPARα and promotes PPARα activity or to any compound that enhances PPARα gene expression.

In some embodiments, the AMPK activator or/and the PPARα agonist is a small organic molecule. The term "small organic molecule" refers to a molecule of a size comparable to those organic molecules generally used in pharmaceuticals. The term excludes biological macromolecules (e. g., proteins, nucleic acids, etc.). Preferred small organic molecules range in size up to about 5000 Da, more in particular up to 2000 Da, and most in particular up to about 1000 Da.

In one embodiment, the AMPK activator according to the invention is thienopyridone derivatives. In one embodiment, the AMPK activator according to the invention is imidazole derivatives. In one embodiment, the AMPK activator according to the invention is furanothiazolidine derivatives. In one embodiment, the AMPK activator according to the invention is metformin. In one embodiment, the AMPK activator according to the invention is troglitazone. In one embodiment, the AMPK activator according to the invention is phenformin. In one embodiment, the AMPK activator according to the invention is galegine. In one embodiment, the AMPK activator according to the invention is resveratrol. In one embodiment, the AMPK activator according to the invention is berberine. In one embodiment, the AMPK activator according to the invention is arctigenin. In one embodiment, the AMPK activator according to the invention is 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR). In one embodiment, the AMPK activator according to the invention is C13. In one embodiment, the AMPK activator according to the invention is antifolate drug. In one embodiment, the AMPK activator according to the invention is methotrexate. In one embodiment, the AMPK activator according to the invention is pemetrexed. In one embodiment, the AMPK activator according to the invention is A-592107. In one embodiment, the AMPK activator according to the invention is A-769662. In one embodiment, the AMPK activator according to the invention is cyclic benzimidazole derivatives. In one embodiment, the AMPK activator according to the invention is pyrrolo [3,2-b]pyridines. In one embodiment, the AMPK activator according to the invention is pyrrolo [2,3-d]pyrimidine derivatives. In one embodiment, the AMPK activator according to the invention is alkene oxindole derivatives. In one embodiment, the AMPK

activator according to the invention is spirocyclic indolinone derivatives. In one embodiment, the AMPK activator according to the invention is 3,3-dimethyl tetrahydroquinoline derivatives. In one embodiment, the AMPK activator according to the invention is thieno [2,3-b]pyridinediones.

Examples of AMPK activator are described in the following patent applications: WO2014128549, WO2006001278, EP1907369, WO2007019914, WO2009124636, WO2007002461, WO2013153479.

In some embodiments, the PPARα agonist is fibrate drugs. In some embodiments, the PPARα agonist is clofibrate. In some embodiments, the PPARα agonist is gemfibrozil. In some embodiments, the PPARα agonist is ciprofibrate. In some embodiments, the PPARα agonist is fenofibrate. In some embodiments, the PPARα agonist is bezafibrate. In some embodiments, the PPARα agonist is GW7647. In some embodiments, the PPARα agonist is GW501516. In some embodiments, the PPARα agonist is Wy 14,643. In some embodiments, the PPARα agonist is rosiglitazone. In some embodiments, the PPARα agonist is pioglitazone. In some embodiments, the PPARα agonist is glitazars. In some embodiments, the PPARα agonist is aleglitazar. In some embodiments, the PPARα agonist is tesaglitazar. In some embodiments, the PPARα agonist is ragaglitazar. In some embodiments, the PPARα agonist is muraglitazar. In some embodiments, the PPARα agonist is KRP-297. In some embodiments, the PPARα agonist is GW-409544. In some embodiments, the PPARα agonist is Ly-510929.

Examples of PPARα agonist are described in the following patent applications: WO02092084, WO2004005266, WO2004020420, WO2004041275, WO2008031500, WO2010071813

Examples of PPARα agonist are described in James E. Klaunig, Michael A. Babich, Karl P. Baetcke, Jon C. Cook, J. Chris Corton, Raymond M. David, John G. DeLuca, David Y. Lai, Richard H. McKee, Jeffrey M. Peters, Ruth A. Roberts & Penelope A. Fenner-Crisp (2003) PPARα Agonist-Induced Rodent Tumors: Modes of Action and Human Relevance, Critical Reviews in Toxicology, 33:6, 655-780.

In one embodiment, nicotinamide riboside, the AMPK activator or/and the PPARα agonist are administered simultaneously, at essentially the same time, or sequentially.

In some embodiments, nicotinamide riboside or/and the AMPK activator or/and the PPARα agonist of the invention is administered to the subject with a therapeutically effective amount.

The terms "administer" or "administration" refer to the act of injecting or otherwise physically delivering a substance as it exists outside the body (e.g., nicotinamide riboside or/and

AMPK activator or/and PPARα agonist of the present invention) into the subject, such as by oral, mucosal, intradermal, intravenous, subcutaneous, intramuscular delivery and/or any other method of physical delivery described herein or known in the art. When a disease, or a symptom thereof, is being treated, administration of the substance typically occurs after the onset of the disease or symptoms thereof. When a disease or symptoms thereof, are being prevented, administration of the substance typically occurs before the onset of the disease or symptoms thereof.

By a "therapeutically effective amount" is meant a sufficient amount of nicotinamide riboside or/and AMPK activator or/and PPARα agonist for the treatment of cardiomyopathy at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific polypeptide employed; and like factors well known in the medical arts. For example, it is well known within the skill of the art to start doses of the compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. However, the daily dosage of the products may be varied over a wide range from 0.01 to 1,000 mg per adult per day. Typically, the compositions contain 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 250, 500 and 1000 mg of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. A medicament typically contains from about 0.01 mg to about 1000 mg of the active ingredient, typically from 1 mg to about 100 mg of the active ingredient. An effective amount of the drug is ordinarily supplied at a dosage level from 0.0002 mg/kg to about 20 mg/kg of body weight per day, especially from about 0.001 mg/kg to 7 mg/kg of body weight per day.

The compositions according to the invention are formulated for parenteral, transdermal, oral, rectal, intrapulmonary, subcutaneous, sublingual, topical or intranasal administration.

Suitable unit administration forms comprise oral-route forms such as tablets, gel capsules, powders, granules and oral suspensions or solutions, sublingual and buccal administration forms, aerosols, implants, subcutaneous, transdermal, topical, intraperitoneal, intramuscular, intravenous, subdermal, transdermal, intrathecal and intranasal administration forms and rectal administration forms.

In one embodiment, the compositions according to the invention are formulated for oral administration.

In one embodiment, nicotinamide riboside is administered orally. In one embodiment, nicotinamide riboside is administered as dietary supplement. For instance, nicotinamide riboside is marketed by Chromadex (Niagen®).

In one embodiment, the compositions according to the invention are formulated for parental administration. The pharmaceutical compositions contain vehicles which are pharmaceutically acceptable for a formulation capable of being injected. These may be in particular isotonic, sterile, saline solutions (monosodium or disodium phosphate, sodium, potassium, calcium or magnesium chloride and the like or mixtures of such salts), or dry, especially freeze-dried compositions which upon addition, depending on the case, of sterilized water or physiological saline, permit the constitution of injectable solutions.

Typically the active ingredient of the present invention (i.e. nicotinamide riboside or/and AMPK activator or/and PPARα agonist) is combined with pharmaceutically acceptable excipients, and optionally sustained-release matrices, such as biodegradable polymers, to form pharmaceutical compositions.

Bypass surgery or stenting with hibernating myocardium or cardiac resynchronization therapy can also be done the subject in need thereof.

The invention will be further illustrated by the following figures and examples. However, these examples and figures should not be interpreted in any way as limiting the scope of the present invention.

FIGURES:

Figure 1. Kaplan-Meier survival curve after myocardial infarction with or without NR administration: Sham animals fed with control diet or NR supplemented diet, pooled together, n=35. Myocardial infarction (MI) group fed with control diet (MI-CD) n=31, or NR diet (MI-NR) n=33. Vertical bullets on top of curves indicate censored events. Kaplan Meier statistics: MI-CD versu Sham, $p<0.0001$; MI-NR versus Sham, $p=0.083$; MI-NR versus MI-CD, $p=0.0467$

Figure 2. Left ventricular ejection fraction at 1 month and 4 months after the surgery. Each individual value is shown by dot. Black circle: CD diet. Black squares: NR diet. Horizontal bar: mean value, vertical error bars: standard error of the mean. ANOVA: MI effect versus SHAM , ¶¶¶¶: $p <0.0001$. NR effect versus CD, §: $p<0.05$. Multiple comparison Tukey test, *: $p<0.05$, ***: $p<0.001$ vs Sham CD.

Figure 3. End-systolic left ventricular internal diameter (LVID) at 1 month and 4 months after the surgery. Each individual value is shown by dot. Black circle: CD diet. Black squares: NR diet. Horizontal bar: mean value, vertical error bars: standard error of the mean. ANOVA: MI effect versus SHAM, ¶¶: p <0.01. Multiple comparison Tukey test: *, p<0.05, ***, p<0.001 vs Sham CD.

Figure 4. Interventricular septum thickness (IVS) at 1 month and 4 months after the surgery. A. End-systolic value. B. End-diastolic value. C. Percentage of thickening of IVS in systole compared to diastole. Each individual value is shown by dot. Black circle: CD diet. Black squares: NR diet. Horizontal bar: mean value, vertical error bars: standard error of the mean. ANOVA: MI effect versus SHAM , ¶: p <0.05, ¶¶: p <0.01. NR effect versus CD, §: p<0.05. Interaction between surgery type and diet type, i: p<0.05. Multiple comparison Tukey test: *: p<0.05, **: p<0.01 vs Sham CD.

Figure 5. Transmitral inflow peak early filling velocity (E wave). Each individual value is shown by dot. Black circle: CD diet. Black squares: NR diet. Horizontal bar: mean value, vertical error bars: standard error of the mean. ANOVA: NR effect versus CD, §§: p<0.01. Multiple comparison Tukey test: #, p<0.05, MI + NR versus versu MI + CD.

EXAMPLE:

Material & Methods and Results

Surgery

A total of 33 rats underwent definitive ligation of the left anterior descending artery (LAD) also called the anterior interventricular branch of left coronary artery left was ligated just after the bifurcation with the circumflex artery to create a myocardial infarction (MI) affecting the interventricular septum and the anterior left ventricular wall. 22 rats underwent a sham operation (Sham) with passage of a suture in the myocardium without ligature. 8 rats died post-operatively: 6 out of 33 in the IM group (18.2%) and 2 out of 22 in the SHAM group (9.1%).

Diet treatment

All surviving rats were immediately challenged with SAFE A04 control diet (CD) or A04 supplemented with 0.7% nicotinamide riboside (NR diet) reaching a dosage ranging from 300 to 600 mg/kg/day depending on rat body weight and food intake.

Survival analysis

The Kaplan-Meier analysis of the survival curves for each group shows that the survival percentage is significantly reduced in the non-treated MI group on control diet (CD) compared

to the SHAM groups (p = 0.037) but not in the MI + NR group, which shows a better survival rate (Figure 1).

Left ventricle echocardiography and doppler analysis

The evolution of cardiac remodelling and function was analyzed by transthoracic echocardiography in time-motion mode and Doppler mode on a Vivid 9 5GE ultrasound system (HealthCare). The analysis of variance (ANOVA) with 2 independent factors, followed by a Tukey test were carried out with the software Graphpad 7.

Heart rate under 2% isoflurane gas anaesthesia did not differ between groups and treatment at either 1 month or 4 months post-surgery and averaged at 350 beats per minutes.

The left ventricular internal diameter in end-systole significantly increased at 1 month and 4 months post-surgery in the MI groups according to the ANOVA analysis (Figure 2, top and bottom panel. The Tukey multiple comparison test showed that this difference is significant only in the MI + CD group but not in the MI + NR group.

The left ventricular ejection fraction (LVEF) was significantly reduced at 1 month in the 2 MI groups although it remained at a higher level in average in the MI + NR group compared to MI + CD group (Figure 3, top panel). At 4 months after the surgery, only the IM-RC group continued to decline with a mean LVEF <40% when the IM + NR group remained stable with a mean LVEF above 50% (Figure 3, bottom panel).

The measurement at end-systole of the thickness of the interventricular septum (IVS) and part of the anterior left ventricular wall that is the most affected by MI showed that the wall was significantly thinner in the MI + CD group at 1 month but not in MI + NR group at 1 month (Figure 4A, left panel). Interestingly, this difference was accentuated after 4 months of remodelling and the ANOVA analysis revealed a significant effect of NR treatment on this parameter (Figure 4A, right panel). The end-diastolic thickness of the IVS was not significantly reduced at 1 month in the IM groups, but there was significant effect of the NR diet to increase IVSd at 4 months (Figure 4B). The percentage of LV wall thickening in systole relative to its thickness in diastole is an indicator of myocardial contractility. This rate of thickening dropped significantly to less than 50% in the MI-CD group while it remained above 50% in the MI-NR group and not significantly different from Sham rats (Figure 4C). Evaluation of the diastolic function was performed by measuring the pulsed Doppler transmitral filling flow on an apical section of the 4 cavities. The positive protodiastolic wave E corresponds to the fast ventricular filling and the end-diastolic wave A to the late atrial contraction. The E wave was not altered at 1 month in any groups (Figure 5, top panel). The NR regimen completely blocked the increase

of the E wave peak in the MI + NR group compared to the MI + CD group at 4 months (Figure 5, bottom panel).

Conclusion

Altogether these data show that the rat model of myocardial infarction that we generated in this study showed increased mortality, left ventricular dilation, reduced ejection fraction falling below 50%, diastolic dysfunction and thinning of the interventricular septal septum as can be seen in human patients. Interestingly, in the MI group fed with NR supplemented diet, starting as soon as 30 minutes after the infarctus and over several months, mortality was reduced, left ventricular ejection was preserved and the infarcted remained thicker, showing signs of better contractility.

NR treatment completely blocked the increase in protodiastolic E wave velocity that was observed in non treated MI group. The peak velocity of E wave that correspond to the blood flowing from left atria to left ventricle in early diastole is mainly influenced by the difference between left atrial pressure and LV pressure at the end of the isovolumic relaxation period in end-systole. As NR had no impact on this parameter in sham group in which the LV wall is intact, it suggests that NR do not increase atrial pressure. Rather, in non-treated MI, the presence of a thin walled infarcted region abnormally increases LV chamber compliance and reduces filling pressure, accelerating the atrial blood inflow (E wave) and this would be counteracted in the NR treated group because of better contractility in the infarcted region, and increased end-systolic thickness of the LV wall maintaining compliance in a more physiological range.

We conclude that chronic NR therapy is efficient to limit mortality, reduce cardiac remodelling and improve cardiac function after myocardial infarction and should be considered in the treatment of human patients suffering ischaemic heart disease.

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Throughout this application, various references describe the state of the art to which this invention pertains. The disclosures of these references are hereby incorporated by reference into the present disclosure.

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CLAIMS:

1. The nicotinamide riboside for use in the treatment of cardiac remodeling in a subject in need thereof.

2. The nicotinamide riboside for use according to claim 1 wherein the cardiac remodelling has appeared after a myocardial infarction (MI), a dilated cardiomyopathy (DCM) a non obstructive cardiomyopathy, a hypertrophic cardiomyopathy, myocarditis, chronic hypertension, congenital heart disease with intracardiac shunting, and valvular heart disease.

3. The nicotinamide riboside for use in the treatment of ischemia, cardiac fibrosis, heart failure or systolic dysfunction caused by a cardiac remodelling or for use in the treatment of a cardiomyopathy when the cause of the cardiac remodelling is the myocardial infarction.

4. The nicotinamide riboside for use according to claims 1 to 3 wherein the nicotinamide riboside is administrated in combination with a therapeutically effective amount of AMPK activator or/and a therapeutically effective amount of PPARα agonist.

5. A therapeutic composition comprising nicotinamide riboside according to the invention for use in the treatment of cardiac remodeling in a subject in need thereof.

6. A method for treating cardiac remodeling in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of nicotinamide riboside.

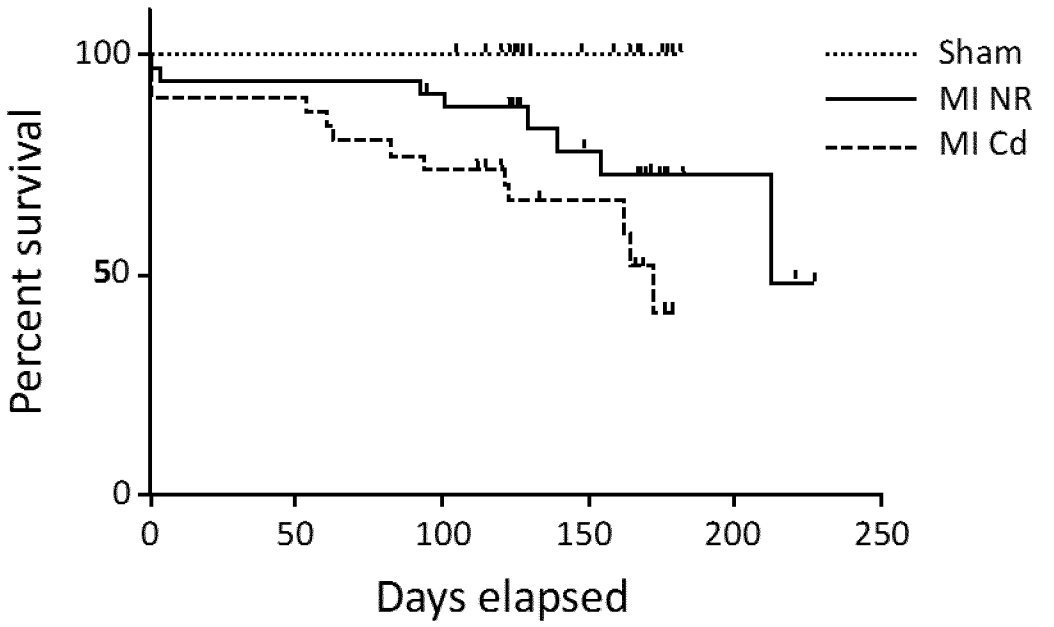

100
50
0
Percent survival
0
50
100
150
200
250
Days elapsed
Sham
MI NR
MI Cd

Figure 1

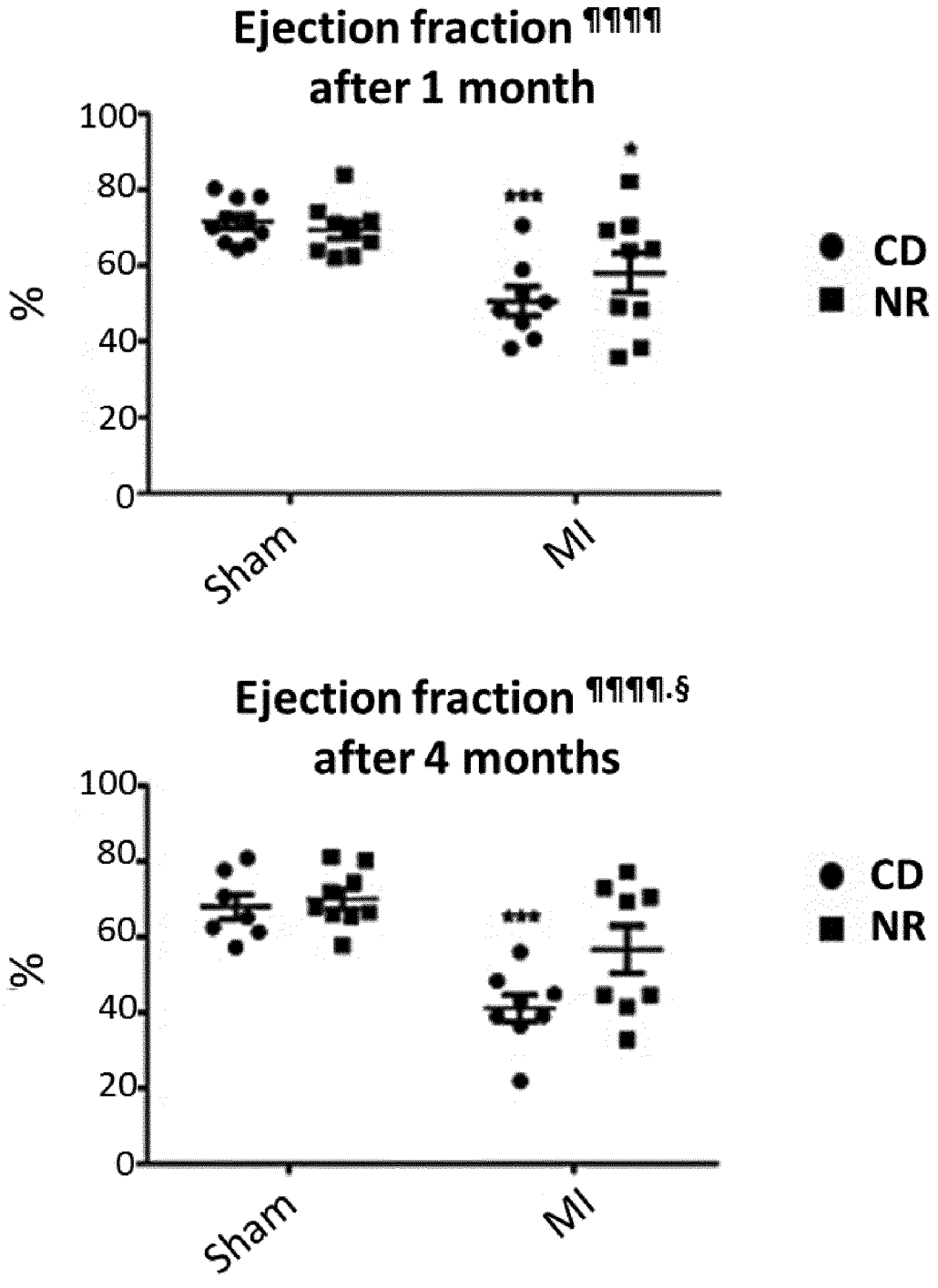

Ejection fraction ¶¶¶¶
after 1 month
100
80
60
40
20
0
%
***
*
Sham
MI
CD
NR
Ejection fraction ¶¶¶¶.§
after 4 months
100
80
60
40
20
0
%
***
Sham
MI
CD
NR

Figure 2

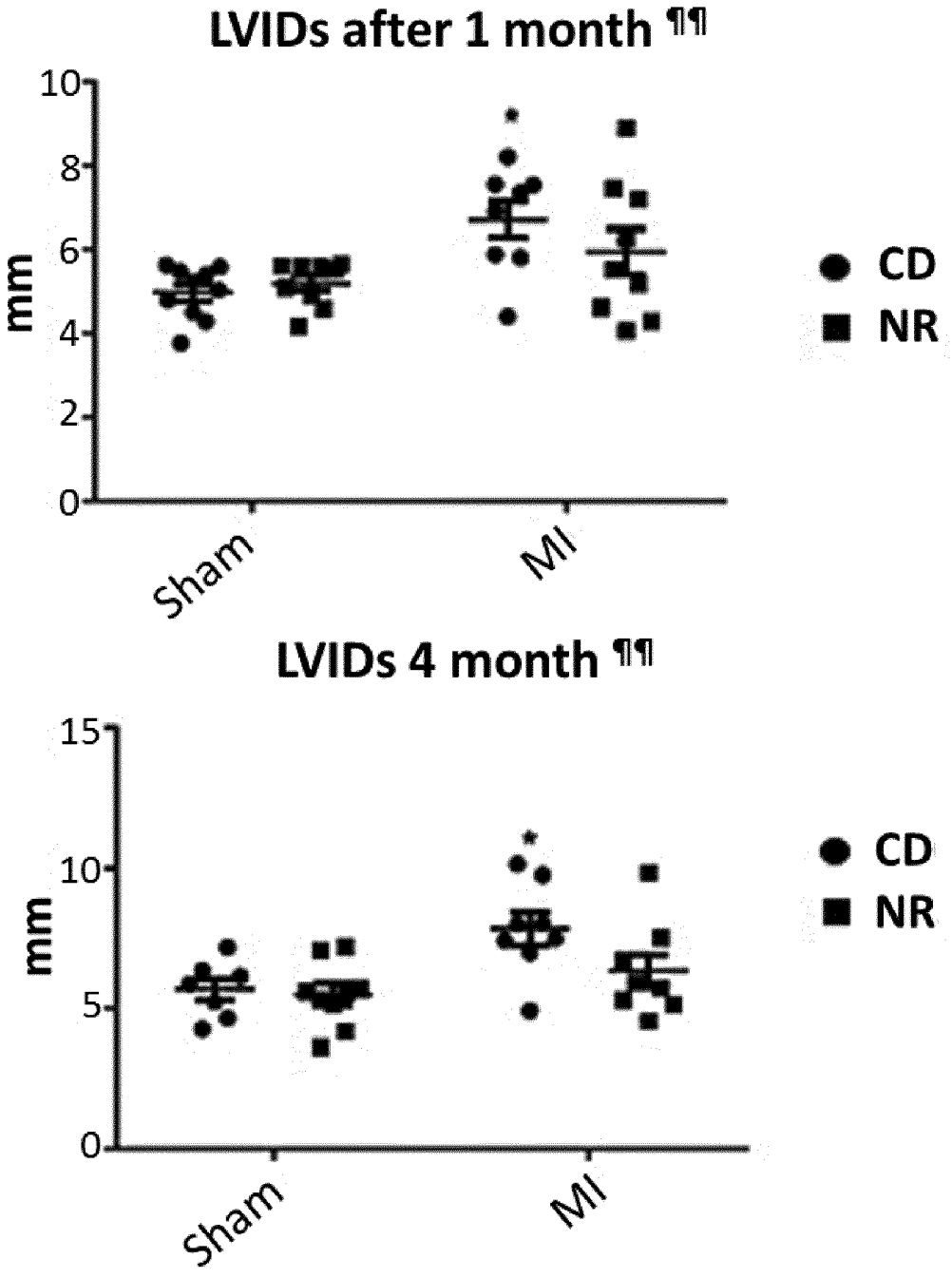

LVIDs after 1 month ¶¶
mm
10
8
6
4
2
0
Sham
MI
CD
NR
LVIDs 4 month ¶¶
mm
15
10
5
0
Sham
MI
CD
NR

Figure 3

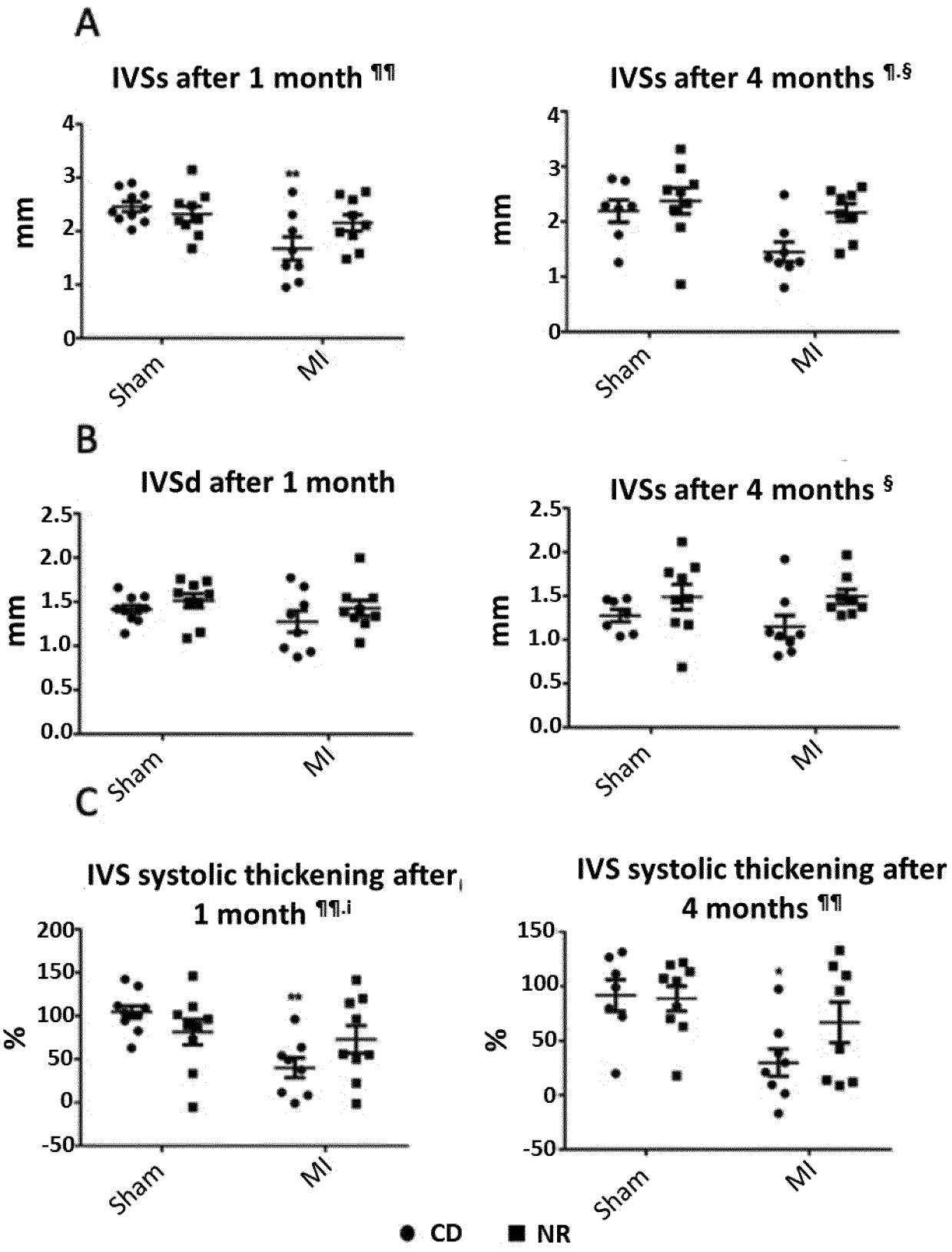

A
IVSs after 1 month ¶¶
IVSs after 4 months ¶.§
mm
Sham
MI
B
IVSd after 1 month
IVSs after 4 months §
C
IVS systolic thickening after 1 month ¶¶.i
IVS systolic thickening after 4 months ¶¶
%
CD
NR

Figure 4

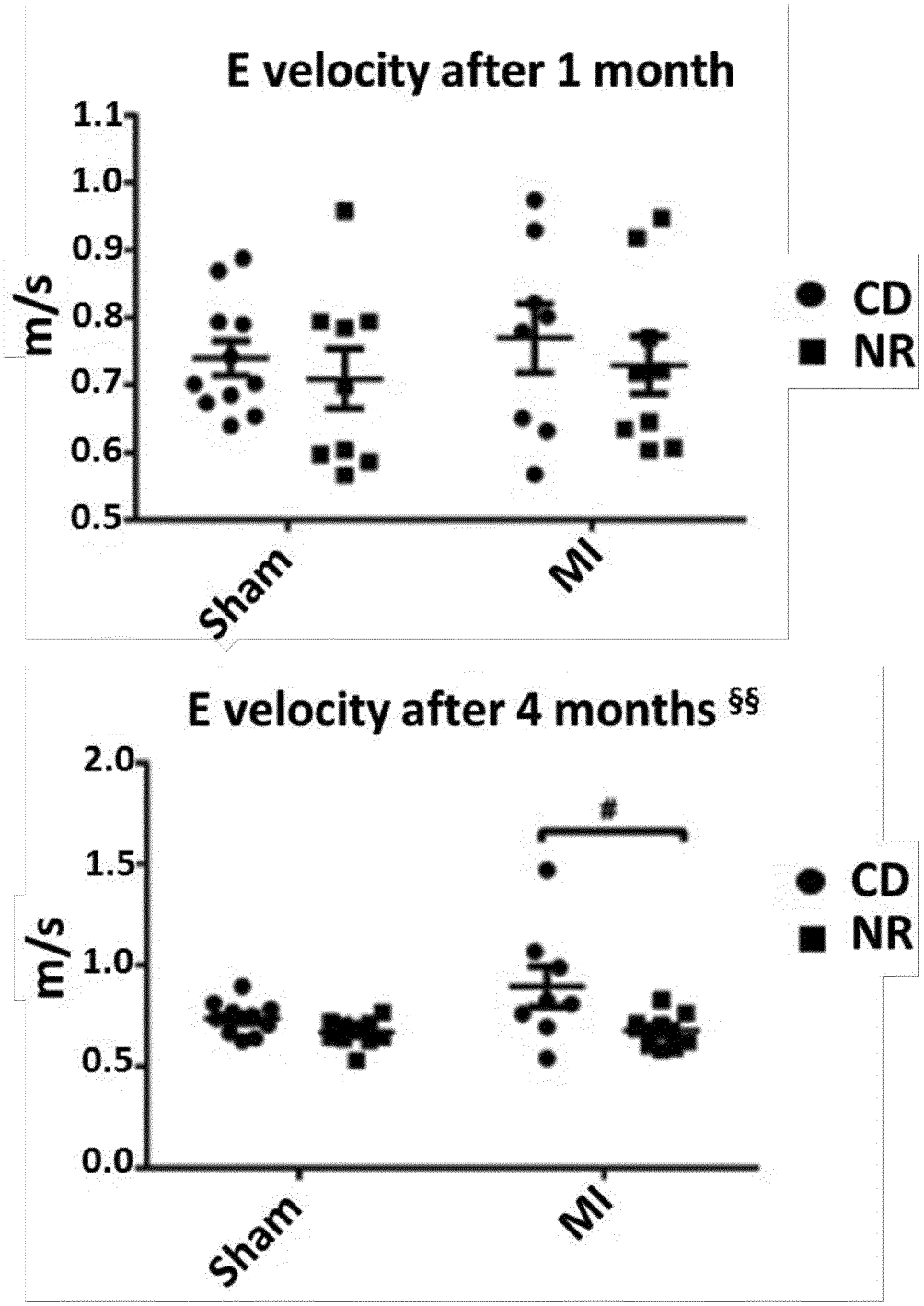

E velocity after 1 month
m/s
1.1
1.0
0.9
0.8
0.7
0.6
0.5
Sham
MI
CD
NR
E velocity after 4 months §§
m/s
2.0
1.5
1.0
0.5
0.0
#
Sham
MI
CD
NR

Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/059081

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/706 A61P9/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/002215 A1 (INSERM [FR]; UNIVERSITÉ PIERRE ET MARIE CURIE (PARIS 6) [FR] ET AL.) 4 January 2018 (2018-01-04) *cf. abstract, page 1, lines 1-21, page 3, lines 16-19 and furthermore line 30 bridging with line 9 at page 4, page 7, lines 6-13, page 34, lines 1-4, page 36, lines 6-27, page 41, lines 1-4, claims*	1-6
X	WO 2016/130691 A1 (UNIV DUKE [US]; UNIV CORNELL [US]) 18 August 2016 (2016-08-18) *cf. abstract, sections [0032] to [0035] at pages 6 and 7, claims*	1-6

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2020	12/05/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stoltner, Anton

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 14 November 2017 (2017-11-14), MA SAI ET AL: "NAD plus Precursor Nicotinamide Riboside Alleviates Alcoholic Cardiomyopathy via Mitophagy Induction: A Novel SIRT3-PGAM5-FUNDC1 Axis", XP009515862, Database accession no. PREV201800710041 abstract ----- MATASIC DANIEL S ET AL: "Emerging potential benefits of modulating NAD(+) metabolism in cardiovascular disease", AMERICAN JOURNAL OF PHYSIOLOGY - HEART AND CIRCULATORY PHYSIOLOGY, vol. 314, no. 4, April 2018 (2018-04), pages H839-H852, XP009515863, *cf. introductive part, in particular 2nd para. of the right-hand col. at front page H839 bridging with first para. of the left col. at page H840, furthermore page H842, 2nd para. of the left-sided col., third para. of the left col. at page H843, last para. of the right-hand col. at page H846, "future directions"* -----	1-6 1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/059081

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018002215 A1	04-01-2018	EP 3478297 A1	08-05-2019
		US 2019350955 A1	21-11-2019
		WO 2018002215 A1	04-01-2018
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		US 2019038647 A1	07-02-2019
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