



(12) **DEMANDE DE BREVET CANADIEN  
CANADIAN PATENT APPLICATION**

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2018/10/02  
(87) Date publication PCT/PCT Publication Date: 2019/04/11  
(85) Entrée phase nationale/National Entry: 2020/04/01  
(86) N° demande PCT/PCT Application No.: IB 2018/057648  
(87) N° publication PCT/PCT Publication No.: 2019/069230  
(30) Priorité/Priority: 2017/10/02 (US62/566,668)

(51) Cl.Int./Int.Cl. *A61K 31/53* (2006.01),  
*A61P 9/00* (2006.01)  
(71) Demandeur/Applicant:  
POXEL, FR  
(72) Inventeur/Inventor:  
HALLAKOU-BOZEC, SOPHIE, FR  
(74) Agent: RIDOUT & MAYBEE LLP

(54) Titre : METHODES DE TRAITEMENT D'UNE INSUFFISANCE CARDIAQUE AVEC FRACTION D'EJECTION PRESERVEE  
(54) Title: METHODS OF TREATING HEART FAILURE WITH PRESERVED EJECTION FRACTION

(57) Abrégé/Abstract:

The present invention provides a method for treating or preventing heart failure with preserved ejection fraction (HFPEF), wherein the method comprises administering to a patient having or at risk of developing HFPEF a therapeutically effective amount of imeglimin.

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

11 April 2019 (11.04.2019)



(10) International Publication Number

WO 2019/069230 A1

## (51) International Patent Classification:

A61K 31/53 (2006.01) A61P 9/00 (2006.01)

## (21) International Application Number:

PCT/IB2018/057648

## (22) International Filing Date:

02 October 2018 (02.10.2018)

## (25) Filing Language:

English

## (26) Publication Language:

English

## (30) Priority Data:

62/566,668 02 October 2017 (02.10.2017) US

(71) Applicant: **POXEL** [FR/FR]; Immeuble Le Sunway, 259/261, Avenue Jean Jaurès, 69007 Lyon (FR).(72) Inventor: **HALLAKOU-BOZEC, Sophie**; c/o Poxel, Immeuble Le Sunway, 259/261, Avenue Jean Jaurès, 69007 Lyon (FR).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

## Published:

- with international search report (Art. 21(3))
- in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE

(54) Title: METHODS OF TREATING HEART FAILURE WITH PRESERVED EJECTION FRACTION

(57) Abstract: The present invention provides a method for treating or preventing heart failure with preserved ejection fraction (HF-PEF), wherein the method comprises administering to a patient having or at risk of developing HFPEF a therapeutically effective amount of imeglimin.



WO 2019/069230 A1

## Methods of Treating Heart Failure with Preserved Ejection Fraction

### Field of the Invention

The present invention relates to the field of medicine, in particular of cardiology. It provides new treatments for heart failure with preserved ejection fraction.

### Background of the Invention

Heart failure (HF) is the leading cause of cardiovascular morbidity and mortality worldwide. It affects about 2% of the western population and 10% of adults aged over 75 years (Lam et al., 2011, Eur. J. Heart Failure 13:18-28). Heart failure is the most common cause of hospitalization in adults over 65 years of age (Lam et al).

HF can be classified according to different criteria such as the side of the heart affected, the severity of the disease, the heart function affected or the phase of the cardiac cycle which is impaired. The cardiac cycle comprises two main phases, the systole and the diastole. Systole is the phase of the cardiac cycle in which the heart is contracting to propel blood out to the body, brain and lungs, whereas diastole is the phase of the cardiac cycle in which the heart is relaxing and filling with incoming blood that is being returned from the body through the inferior vena cava (IVC) and through the superior vena cava (SVC). The better defined type of heart failure is associated with an impairment of the systolic phase. In such a heart failure, the ventricle cannot contract properly which leads to a reduction of the ejection fraction. This type of heart failure is called Heart Failure with Reduced Ejection Fraction (HFREF). Another type of heart failure has been associated with impairment of the diastolic phase. In such a heart failure, the ejection fraction is preserved (Heart Failure with Preserved Ejection Fraction or HFPEF). HFPEF is associated with a decline in diastolic performances of the left ventricle of the heart. Indeed, when the cardiac muscle becomes stiff and loses its ability to relax, the left ventricle cannot readily fill with blood following contraction and the cardiac output either diminishes or remains normal as a result of an elevated ventricular filling pressure. The HFPEF is often characterized histologically by a hypertrophy of cardiomyocytes and increased interstitial collagen deposition and calcium deposition within the myocardium which are assumed to lead collectively to decreased distensibility and LV compliance.

About half of heart failure patients suffer from HFPEF. Indeed, approximately 54% of patients with heart failure (Lam et al; Redfield et al, 2003, Jama 289:194-202; Kitzman et al, 2001, Am. J. Cardiol. 87:413-419; Devereux et al., 2000, Am. J. Cardiol. 86:1090-1096; Ceia et

al., 2002, Eur. J. Heart Failure 4:531-539) and 46-51% of patients hospitalized for acute heart failure have HFPEF (Lam et al; Fonarow et al., 2007, J. Am. College Cardiol. 50:768-777; Yancy et al., 2006, J. Am. College Cardiol. 47:76-84).

Each year, the number of new cases of heart failure is increasing. Indeed, the number of new heart failure cases in the US has increased from 48,000 in 2000 to 670,000 in 2007 (Lam et al; Lloyd-Jones et al., 2010, Circulation 121:586-613), greatly exceeding previous forecasts and suggesting that a further dramatic increase should be expected in the next few decades. Assuming that half the caseload of heart failure consists of HFPEF, an equal increase in HFPEF burden can be projected. Even these may be conservative estimates, since the relative prevalence of HFPEF, as a proportion of the total burden of heart failure cases, is increasing as the population ages (Lam et al; Owan et al., 2005, Prog. Cardiovasc. Dis. 47:320-332), and the survival in patients with HFREF is improving but not in those with HFPEF. Therefore, although already an epidemic, a further dramatic increase in the prevalence of HFPEF is anticipated (Lam et al).

Multiple therapies that provide substantial clinical benefit in HFREF are nowadays available. However, these therapies are not effective in treating or preventing HFPEF (From et al., Cardiovascular Therapeutics, 2011, 29:e6-21). There are currently no effective dietary or pharmacological interventions that improve long-term outcomes in patients with HFPEF (Oghlakian et al., 2011, Mayo Clin Proc. 86:531-539; Komajda M. et al, 2014, Eur. Heart J, 35: 1022-1032). When the chronic condition is tolerable by the patient, the therapy is only directed to alleviating aggravating factors such as high blood pressure. There is thus a strong need for the development of new methods of treating HFPEF. The present invention seeks to meet these and other needs.

## Summary of the Invention

The inventors have surprisingly found that Imeglimin, a triazine derivative, is very effective in treating HFPEF. Indeed, in a model of Zucker fa/fa Rats, a model of metabolic syndrome used for the evaluation of cardiac diastolic dysfunction and in particular HFPEF, the inventors have observed that rats present a great improvement of their diastolic parameters when treated with imeglimin. They particularly noticed a significant reduction of the left ventricular end-diastolic pressure-volume relation in Zucker fa/fa rats after 9 and 90 days of treatment. The left ventricular end-diastolic pressure-volume relation is an index of diastolic dysfunction and left ventricular stiffness and in particular of HFPEF. The reduction of the left ventricular end-

diastolic pressure-volume relation was even of about 26% and 58% after 9 and 90 days of treatment of the Zucker fa/fa rats with imeglimin respectively.

Accordingly, in a first aspect, the present invention concerns a method for treating HFPEF, wherein the method comprises administering to a patient having or at risk of developing HFPEF a therapeutically effective amount of imeglimin.

The invention also concerns, in a second aspect, a method for treating HFPEF, wherein the method comprises administering to a patient having or at risk of developing HFPEF a pharmaceutical composition comprising a therapeutically effective amount of imeglimin and at least one pharmaceutically acceptable carrier.

Preferably, the patient to be treated is a human, more preferably an adult human, preferably of at least 50 years old, more preferably of at least 60 years old, even more preferably of at least 75 years old.

Preferably, the ejection fraction of the patient is superior or equal to 45%, more preferably to 50%, even more preferably to 55%.

Preferably, imeglimin is administered to the patient at a concentration comprised between about 10 mg/kg of body weight/day and about 100 mg/kg of body weight/day, preferably between about 15 mg/kg of body weight/day and about 60 mg/kg of body weight/day, preferably between about 20 mg/kg of body weight/day and about 50 mg/kg of body weight/day, more preferably between about 30 mg/kg of body weight/day and about 45 mg/kg of body weight/day.

Preferably the patient suffers from a metabolic syndrome, preferably selected from the group consisting of obesity and diabetes, in particular type 2 diabetes, monogenic diabetes mellitus, and transient neonatal hyperglycemia.

## Brief Description of the Drawings

25

### **Figures 1A and 1B: Imeglimin treatment improves left ventricle diastolic dysfunction in Zucker fa/fa rats**

Figure 1A: LV End-Diastolic Pressure after nine days (left) or ninety days (right) of treatment of lean rats with vehicle (white boxes), Zucker fa/fa rats with vehicle (black boxes), or Zucker fa/fa rats with imeglimin (crosshatched boxes).

Figure 1B: LV Relaxation Constant Tau after nine days (left) or ninety days (right) of treatment of lean rats with vehicle (white boxes), Zucker fa/fa rats with vehicle (black boxes), or Zucker fa/fa rats with imeglimin (crosshatched boxes).

Figure 1C: LV End-Diastolic Pressure Volume Relation after nine days (left) or ninety days (right) of treatment of lean rats with vehicle (white boxes), Zucker fa/fa rats with vehicle (black boxes), or Zucker fa/fa rats with imeglimin (crosshatched boxes).

\*:  $p < 0.05$  vs lean; †:  $p < 0.05$  vs Zucker with vehicle

5

**Figures 2A and 2B: Imeglimin treatment improves cardiac output and myocardial perfusion in Zucker fa/fa rats**

Figure 2A: Cardiac Output after nine days (left) or ninety days (right) of treatment of lean rats with vehicle (white boxes), Zucker fa/fa rats with vehicle (black boxes), or Zucker fa/fa rats with imeglimin (crosshatched boxes).

10

Figure 2B: Myocardial Perfusion after nine days (left) or ninety days (right) of treatment of lean rats with vehicle (white boxes), Zucker fa/fa rats with vehicle (black boxes), or Zucker fa/fa rats with imeglimin (crosshatched boxes).

\*:  $p < 0.05$  vs lean; †:  $p < 0.05$  vs Zucker with vehicle

**Figure 3: Imeglimin treatment prevents the impairment in acetylcholine-induced relaxation of septal coronary artery of Zucker fa/fa rats**

Figure 3 shows septal coronary relaxation induced by acetylcholine after nine days (left) or ninety days (right) of treatment of Zucker fa/fa rats with vehicle (black circles) or Zucker fa/fa rats with imeglimin (black triangles). Twenty-four weeks-old untreated lean rats (white circle) were used as healthy control.

20

\*:  $p < 0.05$  vs lean rats; †:  $p < 0.05$  vs Zucker with vehicle

### Detailed Description of the Invention

The inventors have surprisingly found that imeglimin is very effective in treating HFPEF. Indeed, in a model of Zucker fa/fa rats, a model of metabolic syndrome used for the evaluation of HFPEF, such rats present a great improvement of their diastolic parameters when treated with imeglimin. The inventors particularly noticed an important reduction of the left ventricular end-diastolic pressure-volume relation in Zucker fa/fa rats after imeglimin treatment. The left ventricular end-diastolic pressure-volume relation is an index of LV compliance, a key factor in HFPEF.

30

## Definitions

As used herein, the terms “Heart failure (HF)”, “congestive heart failure”, “chronic heart failure”, and “acute heart failure” are used interchangeably, and refer to any condition in which the heart is unable to pump blood at an adequate rate or is able to do so only in the presence of increased left ventricular filling pressures. As used herein the term “adequate rate” refers to a rate allowing to supply sufficient blood to meet the needs of the body. When the heart is unable to adequately pump blood to the rest of the body at normal filling left ventricular pressures, blood can back up into the lungs, causing the lungs to become congested with fluid. Typical symptoms of heart failure include shortness of breath (dyspnea), fatigue, weakness, difficulty of breathing when lying flat, and swelling of the legs, ankles or abdomen (edema). Causes of heart failure are related to various disorders including coronary arterial disease, systemic hypertension, cardiomyopathy or myocarditis, congenital heart disease, abnormal heart valves or valvular heart disease, severe lung disease, diabetes, severe anemia hyperthyroidism, arrhythmia or dysrhythmia and myocardial infarction.

Heart failure can occur in the presence of a normal or a reduced left ventricular ejection fraction. As used herein, the terms “Heart Failure with Preserved Ejection Fraction”, “heart failure with normal ejection fraction” or “diastolic heart failure (DHF)”, are equivalent and refer to a patient that suffers from heart failure and that does not present a significant reduction of its left ventricular ejection fraction compared to that of a control (e.g., a healthy individual) or compared to an average value from a healthy population. In certain embodiments, an ejection fraction is classified as normal and a patient suffering from HF is classified as having a HFPEF when the ejection fraction is superior or equal to 40%, preferably superior or equal to 45%, more preferably superior or equal to 50%, still more preferably superior or equal to 55%, yet more preferably superior or equal to 60%. HFPEF usually occurs in older patients with risk factors such as obesity, diabetes and hypertension and is more common in women.

The term “Ejection Fraction”, as used herein, refers to the division of the left ventricle stroke volume by its end-diastolic volume. In other words, the term "ejection fraction" refers to the percentage of blood that is pumped out of a filled ventricle with each heartbeat. Methods for measuring the ejection fraction, for example with an echocardiogram, are well known by a person skilled in the art.

As used herein, the terms “subject”, “individual” or “patient” are interchangeable and refer to an animal, preferably to a mammal, even more preferably to a human. However, the term

“subject” can also refer to non-human animals, in particular mammals such as dogs, cats, horses, cows, pigs, sheep and non-human primates, among others.

As used herein, the term “treatment”, “treat” or “treating” refers to any act intended to ameliorate the health status of patients such as therapy, retardation, delaying the worsening of a disease or disorder. In certain embodiments, such term refers to the amelioration or eradication of a disease or disorder or symptoms associated with said disease or disorder. In other embodiments, this term refers to minimizing the worsening of the disease or disorder resulting from the administration of one or more therapeutic agents to a subject with such a disease or disorder. In a preferred embodiment, the disease or disorder is HFPEF.

As used herein, the terms "prevent," "preventing," and "prevention" refer to a method of preventing the onset of a disease or condition and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, "prevent," "preventing," and "prevention" also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a disease. The terms "prevent," "preventing" and "prevention" may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition.

As used herein, the term “disease” refers to a state of health of a subject wherein the subject cannot maintain homeostasis, and wherein if the disease is not ameliorated then the subject’s health continues to deteriorate.

As used herein, the term “disorder” refers to a state of health of a subject in which the subject is able to maintain homeostasis but in which the subject’s state of health is less favourable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the subject’s state of health.

As used herein, the terms “active principle”, “active ingredient” “active pharmaceutical ingredient”, and “therapeutic agent” are equivalent and refer to a component having a therapeutic effect.

As used herein, the term “therapeutic effect” refers to an effect induced by an active ingredient or by a pharmaceutical composition according to the invention, capable to prevent or to delay the onset or the development of HFPEF, or to cure or to attenuate the effects of HFPEF.

As used herein, the term “excipient or pharmaceutically acceptable carrier” refers to any ingredient except active ingredients that is present in a pharmaceutical composition. Its addition may be aimed at conferring a particular consistency or other physical or gustative properties to the final product.

5       The terms “quantity,” “amount,” and “level” are used interchangeably herein and refer to an absolute quantification of a molecule or ingredient. As used herein, the term “effective amount” refers to a quantity of an active ingredient that is sufficient or effective to prevent, remove or reduce the deleterious effects of a disease or disorder related to HFPEF. The quantity to be administered can be adapted by the person skilled in the art according to the subject to be  
10       treated, to the symptoms of the HFPEF, etc. In particular, doses and regimen of administration may be a function of the nature, the stage and the severity of the HFPEF to be treated, as well as the weight, the age and the global health of the subject to be treated, as well as the judgment of the doctor.

As used herein, the term “diagnosis” refers to the determination as to whether a subject is  
15       likely to be affected with HFPEF.

The term “about” refers to a range of values of  $\pm 10\%$  of the specified value. For example, “about 50” comprises values of  $\pm 10\%$  of 50, i.e. values in the range between 45 and 55. Preferably, the term “about” refers to a range of values of  $\pm 5\%$  of the specified value.

20       In a first aspect, the present invention concerns a method for treating HFPEF, wherein the method comprises administering to a patient having HFPEF a therapeutically effective amount of imeglimin.

In a second aspect, the invention also concerns a method for treating HFPEF, wherein the method comprises administering to a patient having HFPEF a pharmaceutical composition  
25       comprising therapeutically effective amount of imeglimin. In some embodiments, the invention concerns a method for treating HFPEF, wherein the method comprises administering to a patient having HFPEF a pharmaceutical composition comprising therapeutically effective amount of imeglimin as the sole active ingredient. Preferably the pharmaceutical composition further comprises at least one pharmaceutically acceptable carrier.

30

#### **HFPEF Patient**

The methods according to the invention are aimed to treat a patient affected with HFPEF.

The patient is an animal, preferably a mammal, even more preferably a human. However, the patient can also be a non-human animal, in particular mammals such as dogs, cats, horses,

cows, pigs, sheep, donkeys, rabbits, ferrets, gerbils, hamsters, chinchillas, rats, mice, guinea pigs and non-human primates, among others, that are in need of treatment.

The human patient according to the invention may be a child, an infant, an adolescent or an adult, preferably an adult.

5           The human patient according to the invention is preferably an adult of at least 40 years old, more preferably an adult of at least 50 years old, still more preferably an adult of at least 60 years old, yet more preferably an adult of at least 65 years old, even more preferably an adult of at least 70 years old. In a most preferred embodiment, the human patient according to the invention is an adult of at least 75 years old. In some embodiments, the adult is about 40 years  
10   old or older, the adult is about 50 years old or older, the adult is about 60 years old or older, the adult is about 65 years old or older, the adult is about 70 years old or older, or the adult is about 75 years old or older.

          Preferably, the patient is a women.

          Preferably, the patient has been diagnosed with HFPEF.

15           In a first embodiment, a patient is considered as being affected with HFPEF when he suffers from heart failure and presents a preserved ejection fraction, in particular he does not present a significant reduction of its left ventricular ejection fraction compared to that of a control (e.g., a healthy individual) or compared to an average value from a healthy population. Preferably, the ejection fraction of the patient suffering from HFPEF is superior or equal to about  
20   40%, preferably superior or equal to about 45%, more preferably superior or equal to about 50%. Alternatively, the ejection fraction of the patient suffering from HFPEF is superior or equal to about 55%, preferably superior or equal to about 60%.

          In another embodiment, a patient may be considered as being affected with HFPEF when he presents an elevated B-type natriuretic peptide (BNP) level in combination with a normal  
25   ejection fraction. Preferably, a patient has an elevated BNP level when he presents a BNP blood concentration superior to about 35 pg/ml, preferably superior to about 50 pg/ml, more preferably superior to about 75 pg/ml, still more preferably superior to about 100 pg/ml, even more preferably superior to about 200 pg/ml.

          Echocardiography techniques can be used to diagnose diastolic dysfunction and require  
30   measurement of multiple echocardiographic parameters to confirm an HFPEF diagnosis. So a combined approach is needed. Multiple echocardiographic parameters have been proposed as sensitive and specific, including mitral inflow velocity patterns, pulmonary vein flow patterns, E:A reversal, tissue Doppler measurements (i.e., E/E' ratio), and M-mode echo measurements (i.e. of left atrial size). Algorithms have further been developed which combine multiple

echocardiographic parameters. A person skilled in the art is able to choose the most appropriate parameters and/or algorithms.

There are four basic echocardiographic patterns of diastolic dysfunction, which are graded from I to IV:

- 5           - the mildest form is called an “abnormal relaxation pattern”, or grade I diastolic dysfunction. On the mitral inflow Doppler echocardiogram, there is reversal of the normal E/A ratio. This pattern may develop normally with age in some patients, and many grade I patients will not have any clinical signs or symptoms of heart failure;
- 10          - grade II diastolic dysfunction is called “pseudo normal filling dynamics”. This is considered moderate diastolic dysfunction and is associated with elevated left atrial filling pressures. These patients more commonly have symptoms of heart failure, and many have left atrial enlargement due to the elevated pressures in the left heart;
- 15          - grades III and IV diastolic dysfunction are called “restrictive filling dynamics”. These are both severe forms of diastolic dysfunction, and patients tend to have advanced heart failure symptoms:
  - grade III diastolic dysfunction patients will demonstrate reversal of their diastolic abnormalities on echocardiogram when they perform the Valsalva maneuver. This is referred to as “reversible restrictive diastolic dysfunction”;
  - 20          • grade IV diastolic dysfunction patients will not demonstrate reversibility of their echocardiogram abnormalities, and are therefore said to suffer from “fixed, restrictive diastolic dysfunction”.

The presence of either grade III or IV diastolic dysfunction is associated with a significantly bad prognosis. These patients will have left atrial enlargement.

25           Accordingly, in a particular embodiment, a patient may be considered as being affected with HFPEF when he presents a heart failure and a diastolic dysfunction, preferably of at least grade I, more preferably of at least grade II, even more preferably of at least grade III. In a most preferred embodiment, a patient is considered as being affected with HFPEF when he presents a heart failure and a diastolic dysfunction of grade IV.

In a particular embodiment, a patient is considered as being affected with HFPEF if:

- 30          a) the patient presents one or several heart failure typical symptoms, preferably at least 2 heart failure typical symptoms, more preferably at least 3 heart failure typical symptoms, still more preferably at least 4 heart failure typical symptoms, yet more preferably at least 6 heart failure typical symptoms, even more preferably at least 8 heart failure typical symptoms, said symptoms being preferably selected from the

group consisting of shortness of breath or dyspnea, in particular a dyspnea of isolated effort, fatigue, feeling lightheaded, difficulty breathing when lying flat, chronic coughing or wheezing, swelling of the legs, ankles or abdomen (edema), nausea, lack of appetite, confusion or impaired thinking, and high heart rate; preferably the patient presents all these symptoms; and

b) an ejection fraction superior or equal to about 40%, preferably superior or equal to about 45%, more preferably superior or equal to about 50%, still more preferably superior or equal to about 55%, yet more preferably superior or equal to about 60%; and

c) optionally, in particular when the ejection fraction is comprised between about 40% and 50%, a normal end-diastolic volume, preferably inferior to  $97 \text{ ml/m}^2$ , more preferably comprised between  $50 \text{ ml/m}^2$  and  $97 \text{ ml/m}^2$ ; and

d) optionally, in particular when the ejection fraction is comprised between about 40% and 50%, a diastolic function anomaly, preferably evidenced by abnormal echocardiographic parameter(s):

- an  $E/E' > 8$ , preferably an  $E/E' > 12$ , even more preferably an  $E/E' > 13$ ; and
- optionally, in particular when  $8 < E/E' < 12$ , one of the following parameters, preferably two of the following parameters, more preferably all of the following parameters:

- concerning the pulmonary vein flow, an  $Ap-Am > 20 \text{ ms}$ , preferably an  $Ap-Am > 30 \text{ ms}$ ; and
- a dilated left auricle, preferably superior to  $40 \text{ ml/m}^2$ ; and
- a left ventricular hypertrophy, preferably with a left ventricular mass index superior to  $149 \text{ g/m}^2$  for men and superior to  $122 \text{ g/m}^2$  for women; and
- an  $E/A < 0.5$  and a  $TDM > 280 \text{ ms}$ ; and
- an auricle fibrillation; or

- optionally, in particular when  $8 < E/E' < 12$ , a BNP blood concentration superior to  $35 \text{ pg/ml}$ , preferably superior to  $50 \text{ pg/ml}$ , more preferably superior to  $75 \text{ pg/ml}$ , still more preferably superior to  $100 \text{ pg/ml}$ , even more preferably superior to  $200 \text{ pg/ml}$ .

Preferably, the patient further suffers from a metabolic syndrome such as obesity or diabetes, in particular type 2 diabetes, monogenic diabetes mellitus, and transient neonatal hyperglycemia. In some embodiments, the patient further suffers from type 2 diabetes.

Preferably, the patient further suffers from hypertension, elevated fasting plasma glucose,  
5 high serum triglycerides, low high-density lipoprotein (HDL) levels, or a mixture thereof.

The patient can also further suffer from coronary artery disease, systemic hypertension, cardiomyopathy or myocarditis, congenital heart disease, abnormal heart valves or valvular heart disease, severe lung disease, severe anemia hyperthyroidism, arrhythmia or dysrhythmia and myocardial infarction.

10 Preferably, the patient further suffers from endothelial dysfunction

Preferably, the patient has already received a heart failure treatment.

In a particular embodiment, the patient does not have HFPEF but is at risk of developing HFPEF. A patient at risk of developing HFPEF does not necessarily suffer from heart failure. However, he can still present one or several of the heart failure symptoms.

15 A patient at risk of developing HFPEF can be, for example, a patient presenting a diastolic dysfunction of grade I or II as defined above, preferably of grade I, and who does not suffer from heart failure.

A patient at risk of developing HFPEF can also be, for example, a patient who presents some symptoms of heart failure as described above, preferably no more than 2 heart failure  
20 symptom, including but not limited to shortness of breath, leg swelling, and exercise intolerance, and/or one or more other risk factors, including but not limited to:

- a genetic predisposition to HFPEF;
- a family member with HFPEF;
- a myocardial infarction;
- 25 - a cardiomyopathy;
- a ventricular diastolic dysfunction;
- a ventricular systolic dysfunction;
- a ventricular systolic stiffening;
- a vascular stiffening and dysfunction;
- 30 - an endothelial dysfunction;
- a left atrial dysfunction;
- a pulmonary hypertension;
- an autonomic dysfunction (e.g. chronotropic incompetence; sympathetic hyperactivation);

- a skeletal muscle dysfunction (e.g. impaired vasodilation; sympathetic hyperactivation and ergoreflex stimulation); or
- anemia.

Accordingly, in a particular aspect, the invention also concerns a method for preventing HFPEF, wherein the method comprises administering to a patient at risk of developing HFPEF a therapeutically effective amount of imeglimin.

In another particular aspect, the invention also concerns a method for preventing HFPEF, wherein the method comprise administering to a patient at risk of developing HFPEF a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of imeglimin. In another aspect, the invention concerns a method for preventing HFPEF, wherein the method comprise of administering to a patient at risk of developing HFPEF a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of imeglimin as the sole active ingredient. Preferably the pharmaceutical composition further comprises at least one pharmaceutically acceptable carrier.

#### **Imeglimin, pharmaceutical composition, dose, regimen and administration**

The methods according to the invention comprise administering a therapeutically effective amount of imeglimin or a pharmaceutical composition comprising a therapeutically effective amount of imeglimin to the patient.

Imeglimin is a triazine derivative (a tetrahydrotriazine) belonging to the chemical class of the glimins and corresponding to (+)-2-amino-3,6-dihydro-4-dimethylamino-6-methyl-1,3,5-triazine or (6R)-(+)-4-dimethylamino-2-imino-6-methyl-1,2,5,6-tetrahydro-1,3,5 triazine, which may for instance be synthesized as described in WO 2009/095159, WO 2012/072663, WO 2010/012746, WO 2009/141040, or a combination thereof. Imeglimin is also described in U.S. Patent Nos. 7,034,021, 7,452,883, 7,767,676, 7,501,511, 8,227,465, 8,791,115, 8,217,040, 8,461,331, 8,846,911, 9,035,048, 8,742,102, 8,592,370, 8,980,828, 8,742,103, 9,271,984, and 8,937,066.

In some embodiments, imeglimin is administered in the form of a hydrochloride salt. As described herein, the amount of the imeglimin administered to a subject refers to the amount of the imeglimin free base. The embodiments described herein may refer to "imeglimin" when imeglimin hydrochloride is used.

Preferably, the pharmaceutical composition comprises at least one excipient or pharmaceutically acceptable carrier. Conventional excipients can be used according to

techniques well known by those skilled in the art. The pharmaceutical composition comprising imeglimin is formulated in accordance with standard pharmaceutical practice (Lippincott Williams & Wilkins, 2000 and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York) known by a person skilled in the art.

5

Preferably, the treatment with imeglimin or the pharmaceutical composition according to the invention starts no longer than a month, preferably no longer than a week, after the HFPEF has been diagnosed. In a most preferred embodiment, the treatment starts the day of the diagnosis or the day after the diagnosis.

10

The treatment with imeglimin or the pharmaceutical composition according to the invention may be administered as a single dose or in multiple doses, preferably in multiple doses.

Preferably, the treatment is administered regularly, preferably between every day and every week, more preferably every day. In one embodiment, the treatment is administered once a day. In a particular embodiment, the treatment is administered several times a day, preferably 2 or 3 times a day, even more preferably 2 times a day.

15

The duration of treatment with imeglimin or the pharmaceutical composition according to the invention is preferably comprised between 1 day and 50 weeks, more preferably between 1 day and 24 weeks. In a particular embodiment, the treatment lasts as long as the HFPEF persists. In a most preferred embodiment, the treatment is a life treatment.

20

The amount of imeglimin to be administered has to be determined by standard procedure well known by those of ordinary skills in the art. Physiological data of the patient (e.g. age, size, weight, and physical general condition) and the routes of administration have to be taken into account to determine the appropriate dosage, so a therapeutically effective amount will be administered to the patient.

25

In a preferred embodiment, the total imeglimin dose administered per day of treatment with imeglimin or with the pharmaceutical composition according to the invention is comprised between about 500 mg and about 5000 mg, preferably between about 1000 and about 4000, more preferably between about 1500 mg and about 3500 mg, even more preferably between about 2000 mg and about 3000 mg.

30

In another preferred embodiment, imeglimin is administered to the patient at an amount comprised between about 10 mg/kg of body weight/day and about 100 mg/kg of body weight/day, preferably between about 15 mg/kg of body weight/day and about 60 mg/kg of body weight/day, preferably between about 20 mg/kg of body weight/day and about 50 mg/kg of body

weight/day, more preferably between about 30 mg/kg of body weight/day and about 45 mg/kg of body weight/day.

In one embodiment, imeglimin is administered to the patient at a daily dose of about 500 mg, about 1000 mg, about 1500 mg, about 2000 mg, about 2500 mg, about 3000 mg, about 3500 mg, about 4000 mg, about 4500 mg, about 5000 mg, or in a range between any two of the preceding values.

In one embodiment, imeglimin is administered to the patient at a daily dose of 1000 mg, 1500 mg, 2000 mg, 2500 mg, or 3000 mg.

Imeglamin or the pharmaceutical composition according to the invention can be administered by any conventional route of administration, such as topical, enteral, in particular oral or rectal, parenteral, in particular intravenous, intranasal, intramuscular, cutaneous, subcutaneous, or intraocular route of administration and the like.

Preferably, imeglimin or the pharmaceutical composition according to the invention may be administered by enteral or parenteral route of administration. When administered parenterally, the imeglimin or the pharmaceutical composition according to the invention is preferably administered by intravenous route of administration. When administered enterally, imeglimin or the pharmaceutical composition according to the invention is preferably administered by oral route of administration. In a most preferred embodiment, imeglimin is administered orally.

For oral administration, the pharmaceutical composition can be formulated into conventional oral dosage forms such as tablets, capsules, powders, granules, gel capsules, and liquid preparations such as syrups, elixirs, solutions, emulsions, suspensions, and concentrated drops. Nontoxic solid carriers or diluents can be used for oral administration. In some embodiments, imeglimin is administered as tablets.

For compressed tablets, binders, which are agents which impart cohesive qualities to powdered materials, are also necessary. Disintegrants are also usually necessary in tablets to facilitate break-up of the tablet. Moreover, lubricants and glidants can also be included in the tablets to prevent adhesion of the tablet material to surfaces in the manufacturing process and to improve the flow characteristics of the powder material during manufacture. If necessary, the tablet can be coated via the known techniques, in order to mask the taste or to allow enteric dissolution or sustained release of the active principles.

Liquid pharmaceutical forms for oral administration include solutions, suspensions and emulsions. The aqueous solutions can be obtained by dissolving the active principle in water,

followed by addition of flavourings, colorants, stabilisers and/or thickeners, if necessary. In order to improve the solubility, a pharmaceutically acceptable non-aqueous solvent can be added. The aqueous suspensions for oral use can be obtained by dispersing the finely divided active principle in water with a viscous product.

5           The pharmaceutical forms for injection can be obtained, for example, by the following process. The active principle is dissolved, suspended or emulsified either in an aqueous medium or in an oily medium, with a dispersant, a preserving agent, an isotonicity agent, and optionally other additives, such as, if desired, a solubilising agent or a stabiliser.

10           Pharmaceutical forms for external use can be obtained from a solid, semi-solid or liquid composition containing the active principle. For example, to obtain a solid form, the active principle can be treated with excipients and a thickener so as to convert them into powder. The liquid pharmaceutical compositions are prepared in substantially the same way as the forms for injection, as indicated previously. The semi-solid pharmaceutical forms are preferably in the form of aqueous or oily gels or in the form of pomades. These compositions may optionally  
15           contain a pH regulator and a preserving agent.

For transdermal administration, the pharmaceutical composition can be formulated into ointment, cream or gel form and appropriate penetrants or detergents could be used to facilitate permeation.

20           For transmucosal administration, nasal sprays, rectal or vaginal suppositories can be used. The active compound can be incorporated into any of the known suppository bases.

Pharmaceutical compositions according to the invention may be formulated to release the active drug substantially immediately upon administration or at any predetermined time or time period after administration.

25           The pharmaceutical composition of the invention may be administered to a patient by sustained release. Sustained release administration is a method of drug delivery to achieve a certain level of the drug over a particular period of time.

30           In a particular embodiment, the treatment with imeglimin or with the pharmaceutical composition according to the invention is used in conjunction with physical exercise, in particular aerobic exercise training, preferably aerobic exercise training on peak oxygen consumption, and/or with a specific diet, in particular a caloric restriction diet and/or a high nitrate diet.

In some embodiments, imeglimin is administered with a second pharmaceutical agent. In some embodiments, imeglimin is administered concomitantly with the second pharmaceutical

agent. In some embodiments, imeglimin is administered sequentially with the second pharmaceutical agent. The second pharmaceutical agent can be a drug for treating heart failure with reduced ejection fraction, including but not limited to ACE inhibitors, Angiotensin II Receptor Blockers, I<sub>f</sub> Channel Blocker, Diuretics, aldosterone antagonists, beta blockers, statins, and acetylsalicylic acid. The second pharmaceutical agent can also be an antidiabetic drug if the patient suffers from type 2 diabetes. In some embodiments the second pharmaceutical agent is selected from the group consisting of an insulin, an alpha-glucosidase inhibitor, a biguanide, a dopamine agonist, a DPP-4 inhibitor, a glucagon-like peptide, a meglitinide, a sodium glucose transporter (SGLT2 or SGLT1/2) inhibitor, a sulfonylurea, a thiazolidinedione, and a combination thereof.

The form of the pharmaceutical compositions, the route of administration and the dose of administration of imeglimin or of the pharmaceutical composition according to the invention can be adjusted by a person skilled in the art according to the type and severity of the disease, and the patient, in particular its age, weight, sex, and general physical condition.

All the references cited in this application, including scientific articles and summaries, published patent applications, granted patents or any other references, are entirely incorporated herein by reference, which includes all the results, tables, figures and texts of these references.

Although having different meanings, the terms “comprising”, “having”, and “containing” can be replaced one for the other in the entire application.

Further aspects and advantages of the present invention will be described in the following examples, which should be regarded as illustrative and not limiting.

## Examples

## Materials and Methods

### Animals and treatment

Experiments were performed on 12-week-old Male Zucker fa/fa rats or lean control rats purchased from Ch. River (US).

Animals were kept 2 per cage in standard laboratory conditions, and drugs were administered by gavage (at 9 am and at 6 pm) at the dose of 150 mg/kg bid and administered for 9 or 90 days. Imeglimin's effects on cardiac dysfunction were assessed.

5                   • First experiment protocol:

The Zucker fa/fa animals were randomized on their body weight in two groups and three groups were then constituted:

- Lean rats (Treated with vehicle n=12)
- Control Zucker fa/fa rats (Treated with vehicle n=18)
- 10       - Imeglimin treated Zucker fa/fa rats at the dose of 150 mg/kg bid (n=18)

After a short-term treatment (9 days), cardiac function (echocardiography and MRI) and cardiac hemodynamics were assessed (1h after the last treatment) on all rats.

• Second experiment protocol:

15           The Zucker fa/fa animals were randomized on their body weight in two groups and three groups were then constituted:

- Lean rats (Treated with vehicle n=18)
- Control Zucker fa/fa rats (Treated with vehicle n=24)
- Imeglimin treated Zucker fa/fa rats at the dose of 150 mg/kg bid (n=24)

20           After a long-term treatment (90 days), cardiac function (echocardiography and MRI) and cardiac hemodynamics were assessed (1h after the last treatment) on all rats.

### **Preparation of the vehicle and drug suspension**

25           Vehicle: 5g of Methylcellulose were weighed and completely homogenized by stirring in 1 liter of distilled water (during 18h to 24h). The stock solution was stored at 4°C.

The imeglimin suspension was prepared at the concentrations used in the study (150 mg/kg) and homogenized in 10 mL of the Methylcellulose solution. The drug suspension was prepared on the day of administration.

30

### **Body weight and food intake**

Body weight was measured once a week for adjustment of imeglimin treatment concentration.

### **Echocardiography**

Studies were performed on rats after 9 and 90 days of treatment. For this purpose, rats were anesthetized with methohexital, the chest shaved and echocardiograms performed with a Vivid 7 ultrasound echograph equipped with a M12L linear probe operating at 14 MHz and fitted out with Echopac PC software (GE medical) as described previously (Gomez E et al, J Mol Cell Cardiol, 2012, 52: 1257-1264; Vercauteren M et al, Circulation, 2006, 114: 2498-2507). Briefly, a two-dimensional short axis view of the left ventricle was obtained at the level of the papillary muscle, in order to record M-mode tracings. LV diameters were measured by the American Society of Echocardiography leading-edge method from at least 3 consecutive cardiac cycles.

LV outflow velocity was measured by pulsed-wave and cardiac output (CO) was calculated as  $CO = \text{aortic VTI} \times [\pi \times (\text{LV outflow diameter}/2)^2] \times \text{heart rate}$ , where VTI is velocity-time integral.

Measurements were performed by observers blinded to prior results and treatment groups.

### **Myocardial perfusion**

After 9 and 90 days of treatment, basal myocardial perfusion was assessed in methohexital-anesthetized animals using a Bruker Biospec 4.7 Tesla MRI, and using an acquisition T1 sequence that does not need contrast agent application, as previously described (Merabet N et al, J Mol Cell Cardiol, 2012, 52: 660-666; Banquet S et al, Circulation, 2011, 124: 1059-1170.) Briefly, the animals were positioned prone on an actively decoupled and warming pad with hot water circulation was used to maintain its physiological temperature. The ECG signal was monitored by placing two subcutaneous electrodes on each side of the rat at chest level. The electrodes were connected to an ECG trigger unit. As a feature of the trigger unit, both ECG and breath trigger pulses were derived from the observed signal containing both ECG and respiratory EMG signals. After standard adjustments, scout images were acquired to determine the short-axis plane for the perfusion imaging sequence. After optimization of the RF signal, the perfusion sequence was run allowing determination of myocardial tissue perfusion by Arterial Spin Labeling (ASL) technique, in which, the blood in the arteries upstream from the imaging volume is magnetically “labelled”. As a consequence, image intensity changes occur depending on the blood supply to the tissue in the imaged slice. Upon subtraction of an image acquired without spin labelling, the background signal from static spins is removed and the difference image can be used to quantify perfusion. The difference of the inverse of the apparent T1 images

then yields a measure of the regional Cardiac Blood Flow (rCBF) according to  $rCBF = L(1/T1_{sel} - 1/T1_{nonsel})$ , where L is the blood–tissue partition coefficient.

### **Cardiac hemodynamics**

5 Left ventricle function was assessed using left pressure volume curves after 9 or 90 days of treatment, as previously described (Fang Y et al, J Mol Cell Cardiol., 2011, 51:168-176; Fang YH et al, Journal of Cardiovascular Pharmacology, 2012, 59: 260-267). In brief, a 2F miniaturized combined conductance catheter-micromanometer (model SPR-819, Millar Instruments) connected to a pressure-conductance unit (MPCU-200, Millar) was advanced  
10 retrograde via the carotid artery into the left ventricle. This catheter has a micro-manometer surrounded by 4 platinum electrodes; the two outermost electrodes generate a current of 0.1 mA at a frequency of 20 kHz, which is sensed by the two innermost electrodes. Pressure-Volume (PV) loops were recorded at baseline and during loading by gently occluding the abdominal aorta with a cotton swab. Data were stored and analysed by using Millar conductance data  
15 acquisition and analysis software. Finally, the following parameters were measured/calculated from the pressure-volume curves:

- Left ventricular end-diastolic pressure;
- Left ventricular end-systolic pressure;
- Left ventricular relaxation constant Tau;
- 20 - Left ventricular end-diastolic pressure-volume relation; and
- Left ventricular end-systolic pressure-volume relation.

### **Coronary endothelial function**

Coronary endothelial function was assessed after 9 or 90 days of treatment, as described previously (Fang YH et al, Journal of Cardiovascular Pharmacology, 2012, 59: 260-267 ; Mulder  
25 et al., Eur Heart J., 2008, 29:2171-2179). In brief, at the end of the left ventricular function assessment, the heart was removed and immediately placed in cold oxygenated Krebs buffer. A 1.5- to 2-mm-long segment of arteries were carefully dissected and mounted in a small vessel myograph. Normalization procedure was performed after an equilibration period. Segments with an internal diameter <170  $\mu$ m was excluded to avoid mechanical endothelial injury and  
30 unspecific dysfunction. Concentration-response curves to acetylcholine ( $10^{-8}$  to  $3 \times 10^{-5}$  mol/L) were performed in serotonin-precontracted segments ( $10^{-5}$  mol/L).

### **Cardiac Histology**

At the end of the treatment period, the heart was taken out. After fixation, the left ventricle was cut in 3 sections of identical thickness. The sections of the heart were dehydrated and embedded in paraffin. 3µm-thick sections were cut from each block and mounted on glass slides. Sections were stained with Sirius red for the determination of collagen. Slides were enlarged 500 times using a microscope connected to an image analysis system, as previously described (Mulder et al., J.Am.Coll.Cardiol., 1997). Collagen density was calculated in the left ventricle as the surface occupied by collagen divided by the surface of the image.

### **Plasma nitrite levels**

Plasma nitrite measurements as a marker of NO production was performed using tri-iodide based chemiluminescence. The NO signal was quantified using a nitric oxide analyzer (NOA™ 280, Sievers Instruments Inc., Boulder, CO, USA).

### **Left ventricular oxidative stress**

Left ventricular reactive oxygen species production level were evaluated in left ventricular homogenates (obtained after 9 or 90 days of treatment) by electron paramagnetic resonance spectroscopy (EPR) using the spin probe 1-hydroxy-3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidine (CMH, Noxygen, Germany), as previously described (Mulder P, Eur Heart J. 2008;29:2171-2179). Stock solution of CMH (50 mM) were prepared in Krebs-HEPES buffer (0.1 M NaCl, 5 mM KCl, 2.5 mM CaCl<sub>2</sub>, 1.2 mM MgSO<sub>4</sub>, 25 mM NaHCO<sub>3</sub>, 1 mM KH<sub>2</sub>PO<sub>4</sub>, 5.6 mM D(+)-Glucose, 20 mM Na-HEPES, pH 7.4) containing 25 µM deferoxamine and 5 µM diethyldithiocarbamate. This stock solution of CMH was deoxygenated prior to the experiment in order to prevent CMH oxidation. After one hour of incubation in Krebs-HEPES buffer containing 2 mM ADP and the mitochondrial respiratory substrates, 10 mM glutamate and 4 mM malate, samples were frozen in a syringe in liquid nitrogen and kept at -80°C until analysis. The oxidation of CMH into the stable 3-methoxycarbonyl-proxyl (CM•), driven mainly by superoxide and peroxynitrite reactions, was recorded using a MiniScope MS-200 X-band spectrometer (Magnettech, Germany). The EPR instrumental setting for field scan were as follows: Bo-field 3356.98 G, microwave power 1 mW, microwave attenuation 20 dB, modulation frequency 9.74 GHz, modulation amplitude 5 G, scan time 60 sec. Intensity of the spectra was measured from the height of the central line. CM• production was quantified using CP° standard and expressed in µmol of CM• per mg of total proteins.

### **Statistical analysis**

All results are given as mean  $\pm$  SEM.

In order to evaluate the effect of metabolic syndrome, all parameters obtained in untreated Zucker fa/fa and lean rats were compared by Student's unpaired two-tailed t-test. In order to evaluate the effects of long- or short-term imeglimin treatment, all parameters obtained in 9- and 90-day treated Zucker fa/fa rats were compared with time-matched untreated Zucker fa/fa using Student's unpaired two-tailed t-test.

Before applying parametric tests as Student's unpaired two-tailed t-test, the Gaussian distribution of data was assessed by Shapiro-Wilk normality test and Kolmogorov-Smirnov test and graphically by QQplot and normal probability plot.

## **Results**

This preclinical study in a rat model of metabolic syndrome was designed to investigate imeglimin's protective effects on HFPEF. Indeed, obese Zucker fa/fa rats are known to develop cardiac dysfunctions which are very similar to the ones of HFPEF patients. The Zucker fa/fa rats were treated with 150 mg/kg imeglimin twice-daily for 9 or 90 days.

13 and 24 weeks old untreated Zucker fa/fa rats present:

- Left Ventricle diastolic dysfunction:
  - an increased LV end-diastolic pressure (cf. Figure 1A);
  - an increased LV relaxation constant Tau (cf Figure 1B); and
  - an increased LV end-diastolic pressure volume relation (cf. Figure 1 C).
- associated with reduced cardiac output (cf Figure 2A) and myocardial perfusion (cf. Figure 2B).

These parameters are typical of HFPEF.

When Zucker fa/fa rats were treated with imeglimin during 90 days, a significant reduction of LV end-diastolic pressure (Figure 1A), LV relaxation constant Tau (Figure 1B) and LV end-diastolic pressure volume relation (Figure 1C) were observed as well as an increased cardiac output and myocardial perfusion (cf. Figures 2A and 2B).

In particular, the increase in the myocardial perfusion and the reduction of the left ventricular end-diastolic pressure-volume relation were already significant after only 9 days of treatment.

The LV compliance was increased by about 50% after 90 days of treatment.

Moreover, imeglimin treatment was shown to improve coronary artery endothelium-dependent relaxation. Indeed, imeglimin administration for 9 and 90 days prevented the impairment in acetylcholine-induced relaxation of septal coronary artery observed in untreated Zucker fa/fa rats at 90 days (cf. Figure 3).

In addition, the results show that LV interstitial collagen was significantly increased in 24-week old Zucker fa/fa rats when compared to lean rats (cf. Table 1). A 90-day administration of imeglimin significantly reduced LV collagen density (cf. Table 1). This reduced LV collagen accumulation probably contributes to the further improvement of LV compliance after long-term treatment with imeglimin.

LV reactive oxygen species (ROS) production was also increased, while plasma nitrite levels were decreased in 13- and 24-week-old untreated Zucker fa/fa rats when compared to lean rats (cf. Table 1). Both 9- and 90-day imeglimin treatment decreased ROS levels and increased plasma nitrite levels (cf. Table 1).

This observed reduction in LV tissue ROS production limits the neutralization of NO, resulting in an increased NO bio-availability as suggested by the increase of plasma nitrites. This increase of NO bio-availability likely contributes to the immediate improvement of LV diastolic dysfunction via direct and indirect mechanisms. Indeed, reduced myocardial NO bioavailability increases myocyte resting tension and impairs LV dysfunction (Van Heerebeek et al., *Circulation.*, 2008, 117:43-51 ; Gillebert et al., *Am J Physiol.*, 1992, 263:H857-865 ; Van Heerebeek et al., *Curr Diab Rep.*, 2009, 9:79-86), while an increase in NO bio-availability/production induced via administration of its co-factor tetrahydrobiopterin, NO donors or endothelial NO synthase enhancers improves LV diastolic dysfunction (Silberman et al., *Circulation.*, 2010, 121:519-528; Matter et al., *Circulation.*, 1999, 99:2396-2401; Fraccarollo et al., *Circulation.*, 2008, 118:818-827). Furthermore, an improved NO-bio-availability at the level of the coronary vasculature, as illustrated by the improvement of coronary endothelium dependent dilatation, might contribute to the improvement of LV diastolic dysfunction, via the increase in myocardial tissue perfusion observed after imeglimin treatment. Indeed, the normalization of myocardial perfusion by imeglimin probably prevents LV tissue hypoxia observed in Zucker fa/fa rats and subsequent activation of mechanisms inducing LV dysfunction.

**Table 1:**

Group	Time	Lean	Zucker fa/fa	
			Untreated	Imeglimin
LV collagen density (%)	D <sub>9</sub>	-	-	-
	D <sub>90</sub>	2.06±0.11	3.07±0.09*	2.52±0.20†
LV ROS production (AU.µg <sup>-1</sup> .h <sup>-1</sup> )	D <sub>9</sub>	32.75±0.97	39.51±1.77*	27.61±1.29†
	D <sub>90</sub>	26.69±3.06	40.96±3.29*	34.02±1.49†
Plasma nitrite (mM)	D <sub>9</sub>	407±20	270±27*	424±15†
	D <sub>90</sub>	450±43	292±27*	438±18†

\*: p<0.05 vs. Lean Zucker fa/+; †: p<0.05 vs. untreated Zucker fa/fa

5 This study demonstrates that very early in the course of treatment, imeglimin strongly improved the parameters of LV diastolic dysfunction in the Zucker fa/fa rats compared to untreated Zucker fa/fa rats, underlying a clear beneficial effect of imeglimin on the progression of HFPEF.

We claim:

1. A method for treating or preventing heart failure with preserved ejection fraction (HFPEF), wherein the method comprises administering to a patient having or at risk of developing  
5 HFPEF a therapeutically effective amount of imeglimin.
2. A method for treating or preventing HFPEF, wherein the method comprises administering to a patient having or at risk of developing HFPEF a pharmaceutical composition comprising a therapeutically effective amount of imeglimin and at least one pharmaceutically acceptable  
10 carrier.
3. The method according to claim 1 or 2, wherein the patient is a human, preferably an adult human.
- 15 4. The method according to claim 3, wherein the patient is a female human.
5. The method according to claim 3 or 4, wherein the patient is at least 50 years old, preferably at least 60 years old, more preferably at least 75 years old.
- 20 6. The method according to any one of claims 1 to 5, wherein the ejection fraction of the patient is superior or equal to 45%, preferably to 50%, more preferably to 55%.
7. The method according to any one of claims 1 to 6, wherein the imeglimin is administered to the patient at an amount between about 10 mg/kg of body weight/day and about 100 mg/kg  
25 of body weight/day, preferably between about 15 mg/kg of body weight/day and about 60 mg/kg of body weight/day, preferably between about 20 mg/kg of body weight/day and about 50 mg/kg of body weight/day, more preferably between about 30 mg/kg of body weight/day and about 45 mg/kg of body weight/day.
- 30 8. The method according to any one of claims 1 to 6, wherein the amount of imeglimin is about 500 mg to about 3000 mg per day.

9. The method according to claim 8, wherein the amount of imeglimin is about 1000 mg to about 3000 mg per day.

10. The method according to any one of claims 1 to 9, wherein imeglimin is administered orally.

11. The method according to any one of claims 1 to 10, wherein imeglimin is administered once, twice, or three times per day.

12. The method according to claim 11, where imeglimin is administered once per day.

13. The method according to any one of claims 1 to 12, where imeglimin is administered in the form of a free base or a pharmaceutically acceptable salt thereof.

14. The method according to claim 13, where imeglimin is administered in the form of a hydrochloride salt.

15. The method according to any one of claims 1 to 14, wherein the patient suffers from a metabolic syndrome, preferably selected from the group consisting of obesity and diabetes, in particular type 2 diabetes, monogenic diabetes mellitus, and transient neonatal hyperglycemia.

16. The method according to claim 15, wherein the patient suffers from type 2 diabetes.

17. The method according to any one of claims 1 to 16, wherein imeglimin is administered with a second pharmaceutical agent.

18. The method according to claim 17, wherein imeglimin is administered concomitantly with the second pharmaceutical agent.

19. The method according to claim 17, wherein imeglimin is administered sequentially with the second pharmaceutical agent.

20. The method according to any one of claims 17 to 19, wherein the second pharmaceutical agent is an antidiabetic drug.

21. The method according to claim 20, wherein the second pharmaceutical agent is selected from the group consisting of an insulin, an alpha-glucosidase inhibitor, a biguanide, a dopamine agonist, a DPP-4 inhibitor, a glucagon-like peptide, a meglitinide, a sodium glucose transporter (SGLT2 or SGLT1/2) inhibitor, a sulfonylurea, a thiazolidinedione, and a combination thereof.
- 5

1/6

## LV End-Diastolic Pressure

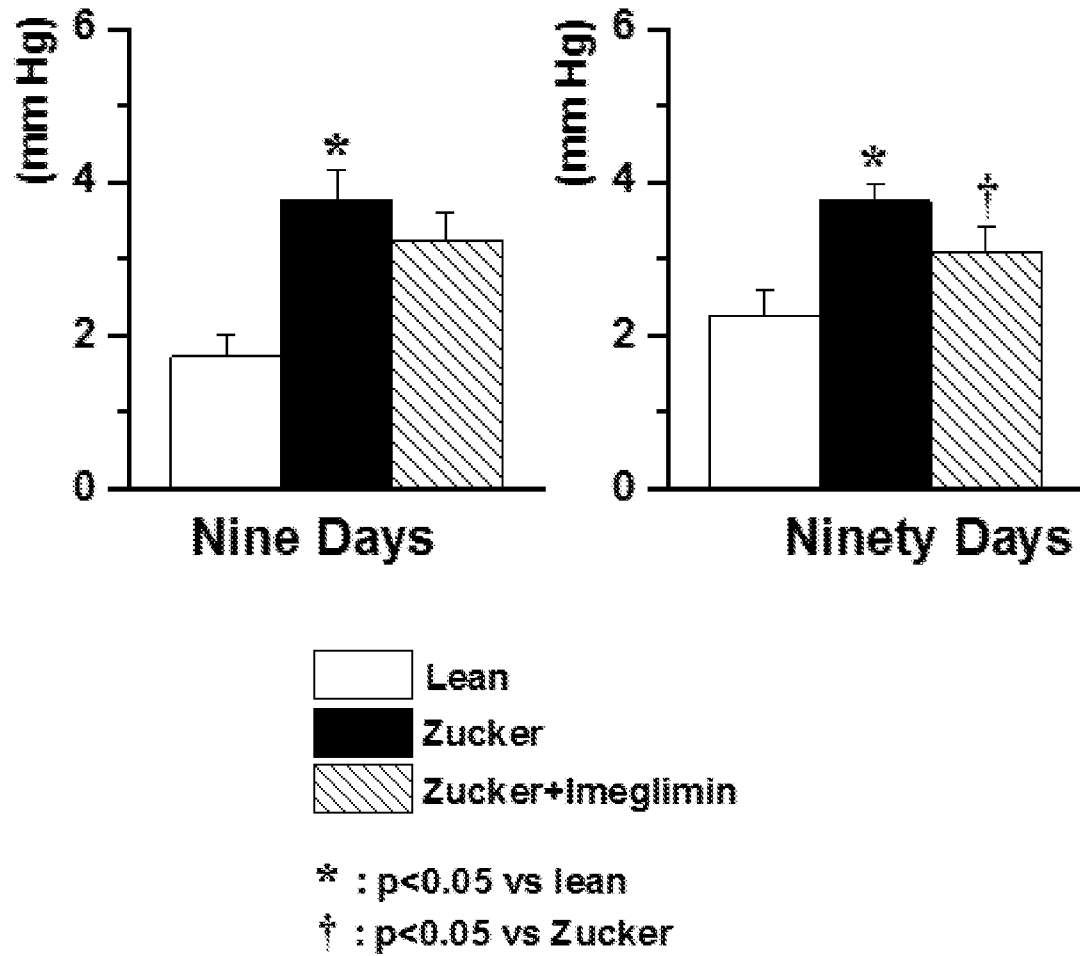
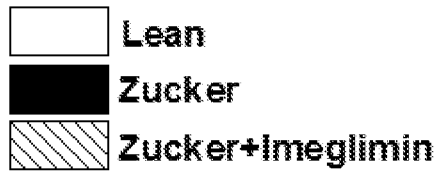
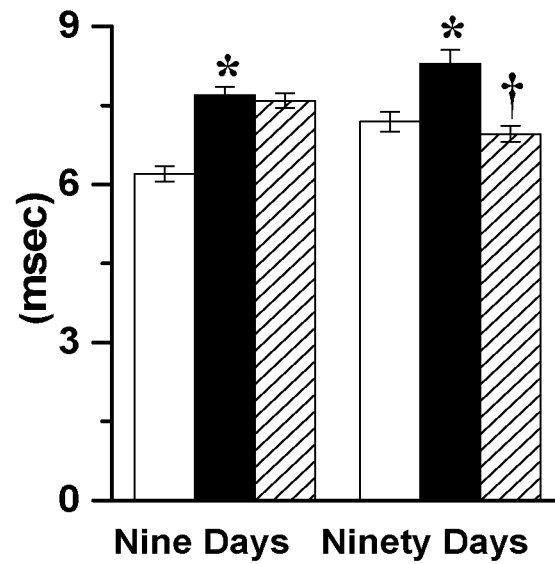


Figure 1A

2/6

## LV Rel. Const. Tau



\* : p<0.05 vs lean

† : p<0.05 vs Zucker

Figure 1B

3/6

## LV End-Diastolic Pressure Volume Relation

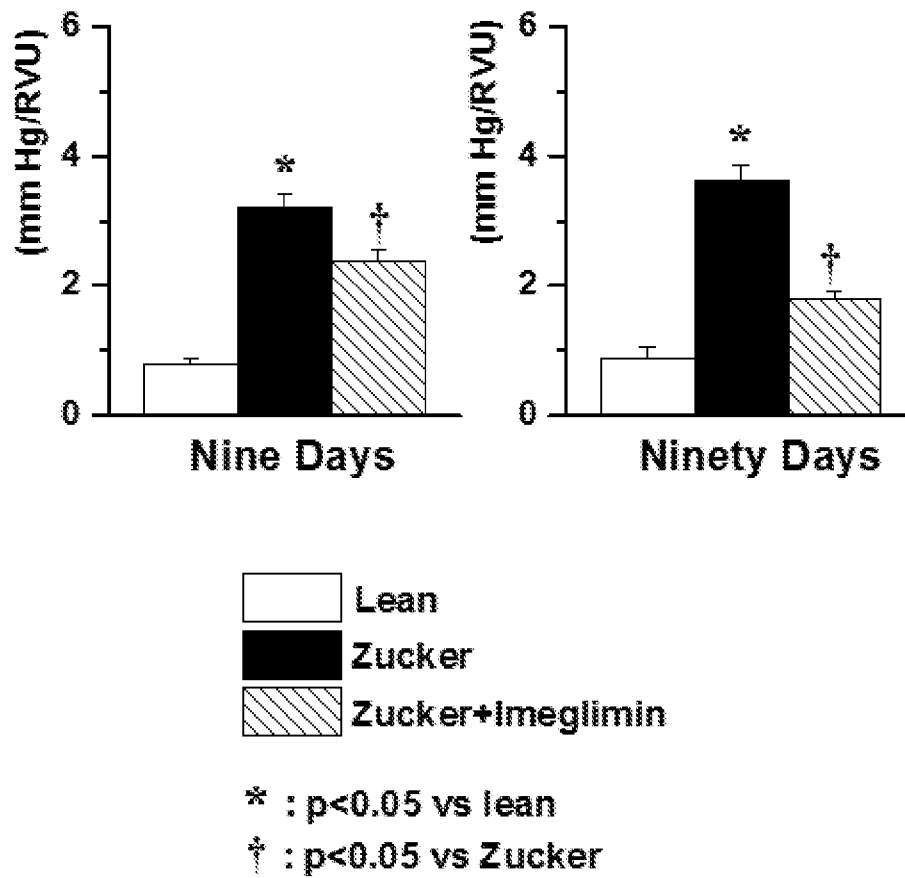
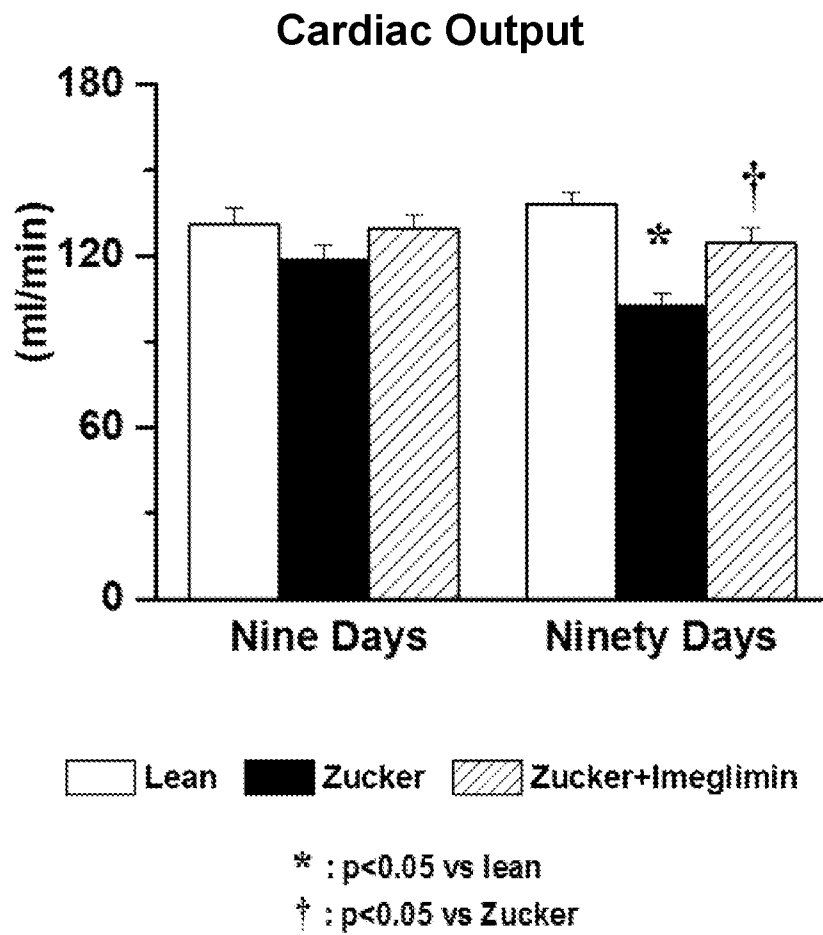
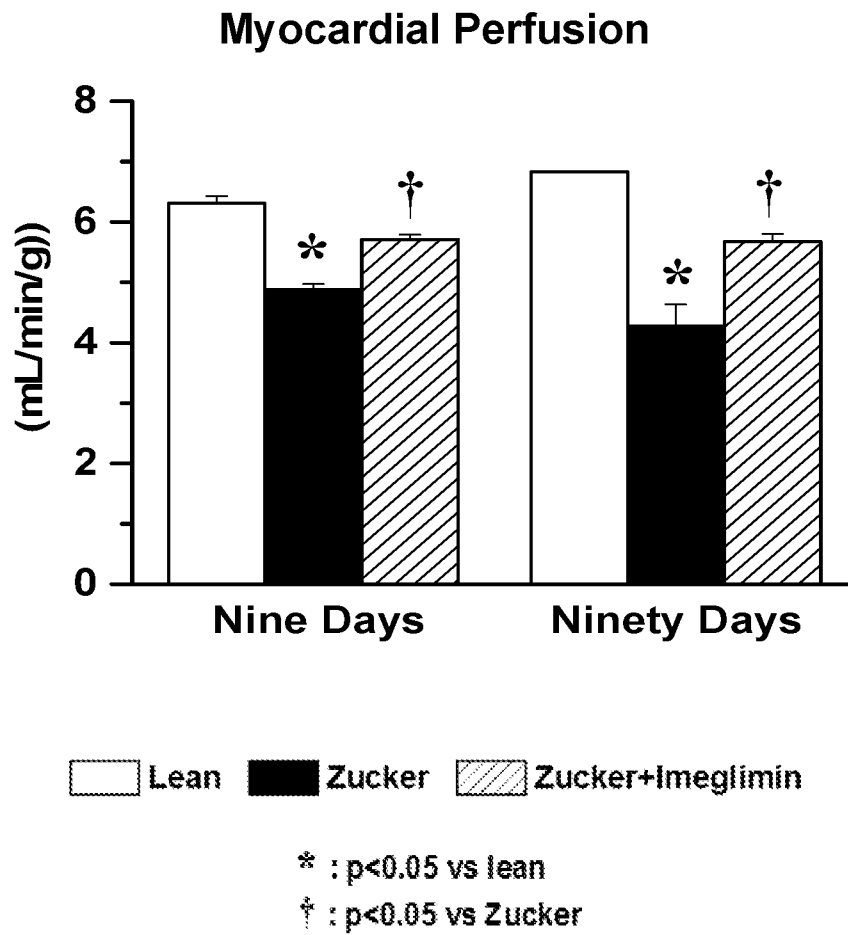


Figure 1C

4/6

**Figure 2A**

5/6

**Figure 2B**

6/6

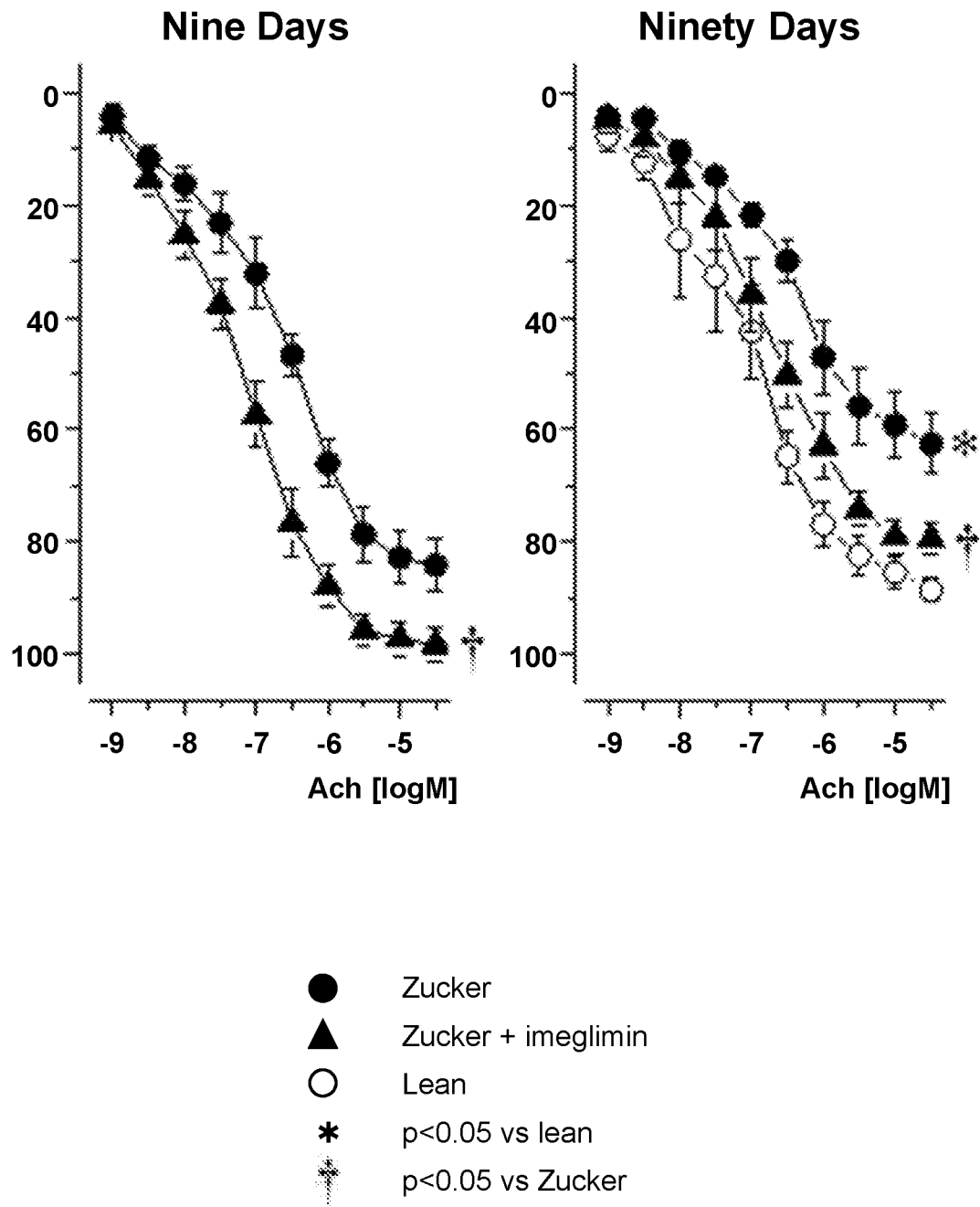


Figure 3